

Draft Comparative Effectiveness Review

Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

Prepared for:

Agency for Healthcare Research and Quality
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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an already-established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that systematic Comparative Effectiveness Reviews will be helpful not only to government programs but also to individual health plans, providers, and purchasers, and to the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that the greatest range of decision makers possible (and that includes consumers who make decisions about their own and their family's health) can benefit from the evidence. Therefore, all Comparative Effectiveness Reviews are accompanied by information tailored to the public.

Work under this program is transparent and user driven. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

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This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0024). The findings and conclusions in this document are those of the authors who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decision-makers; patients and clinicians, health system leaders, and policymakers, make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

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Comparative Effectiveness and Safety of Analgesics for Osteoarthritis

Executive Summary

Prepared for the Effective Health Care Program

Agency for Healthcare Research and Quality, U.S. Department of Health and
Human Services

The Effective Health Care program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions for treating difficult health problems. The object is to help consumers, health care providers and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high priority health conditions. It also promotes and generates new scientific evidence, by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at
www.effectivehealthcare.ahrq.gov.

Background

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life. Among U.S. adults aged 30 years or older, approximately 6% have symptomatic osteoarthritis of the knee, and 3% have symptomatic osteoarthritis of the hip. Osteoarthritis increases with age, with the incidence and prevalence increasing 2- to 10-fold from age 30 to 65, and continues to increase after age 65. The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product, with more than half of these costs related to work loss.

Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Commonly used over-the-counter supplements include glucosamine and chondroitin. Topical agents frequently used by patients with osteoarthritis are rubefacients (including capsaicin), NSAIDs, and other miscellaneous preparations. Opioid medications are also frequently used for patients with chronic pain, especially if it is refractory to other therapies, but are usually not recommended for first-line treatment for osteoarthritis or other conditions because of risks of addiction, tolerance, diversion, and other adverse events. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs

within a class. Non-pharmacologic interventions (such as physical therapy, weight reduction, and exercise) are also available to treat pain and potentially improve functional status in patients with osteoarthritis.

NSAIDs have analgesic, anti-inflammatory, and anti-pyretic effects by blocking cyclo-oxygenases (COX), enzymes that are needed to produce prostaglandins. Most NSAIDs block two different cyclo-oxygenases, called COX-1 and COX-2. COX-2, found in joint and muscle, contributes to pain and inflammation. Because they block COX-2s, NSAIDs reduce pain significantly in patients with arthritis, low back pain, minor injuries, and soft tissue rheumatism compared with placebo.

A challenge in treating osteoarthritis is determining which medications will provide the greatest symptom relief with the fewest serious adverse effects. Non-specific NSAIDs cause gastrointestinal bleeding because they block the COX-1 enzyme, which protects the lining of the stomach from acid. In the US, complications from NSAIDs are estimated to cause about six deaths per 100,000 population, a higher death rate than that for cervical cancer or malignant melanoma. Conversely, COX-2 specific medications (also called coxibs) have been associated with increased rates of serious cardiovascular and other adverse effects.

This report summarizes the available evidence comparing the benefits and safety of analgesics in the treatment of osteoarthritis. Questions addressed in this report are:

1. What is the evidence for benefits and harms of treating osteoarthritis with oral medication(s)? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? (*Note: This question addresses the therapeutic benefits of long-term use for only the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including use for other labeled indications such as the treatment of rheumatoid arthritis.*)
2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?
 - Demographic subgroups include age, sex, and race.
 - Co-existing diseases include hypertension, edema, ischemic heart disease, heart failure; PUD; history of previous bleeding due to NSAIDS.
 - Concomitant medication use includes anticoagulants.
3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors (PPIs)?
4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations? Topical preparations include: capsaicin, diclofenac, ibuprofen, ketoprofen and salicylate.

A summary of the findings is shown in the Table A.

Conclusions

Benefits

- Non-selective NSAID vs. non-selective NSAID
 - No clear difference in efficacy found between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac).
 - No difference between salsalate and aspirin in one short-term trial.
 - No evidence for salsalate or aspirin vs. non-aspirin NSAID.
- COX-2 selective vs. non-selective NSAID
 - No clear difference found from many good-quality, published trials.
- Celecoxib vs. rofecoxib
 - Consistent evidence from six good-quality, published trials found no clinically significant differences at commonly used doses.

Harms

- Gastrointestinal (GI) and cardiovascular (CV) safety: Rofecoxib
 - In the only large, long-term trial (VIGOR), rofecoxib 50 mg daily caused fewer serious ulcer complications compared with naproxen in patients with RA, but also significantly increased the risk of myocardial infarction. The overall rate of serious adverse events was higher with rofecoxib compared with naproxen.
 - There was one fewer symptomatic ulcer for every 62 patients treated with rofecoxib, and one fewer serious complication for every 191 patients.
 - One additional myocardial infarction occurred for every 333 patients treated with rofecoxib.
 - An increased risk of myocardial infarction was also found in a systematic review of rofecoxib and in a polyp prevention trial.
- GI and CV safety: Celecoxib
 - In a good-quality meta-analysis of all known arthritis trials, most of which evaluated short-term use, celecoxib caused fewer ulcer complications than non-selective NSAIDs and did not increase the risk of myocardial infarction.
 - It is not clear whether celecoxib is safer than non-selective NSAIDs when used longer than 3-6 months. In the only large, published trial (CLASS), celecoxib at 800 mg daily did not decrease serious ulcer complications compared with diclofenac and ibuprofen overall; the risk of serious GI events was lower compared with ibuprofen, but not diclofenac at 6 months in patients who did not use aspirin; and there was no reduction in serious GI events at the end of follow-up. The overall rate of serious adverse events with celecoxib was similar to ibuprofen and diclofenac.
 - Fair-quality evidence on longer-term safety of celecoxib is primarily based on observational studies and are largely consistent with the results of short-term trials.
 - Celecoxib was associated with an increased risk of myocardial infarction in one long-term trial of polyp prevention.
- GI and CV safety: Valdecoxib
 - Valdecoxib was associated with a lower risk of upper GI complications compared with non-selective NSAIDs.
 - Two short-term trials in a high-risk post-coronary artery surgery setting found

that valdecoxib was associated with a two- to three-fold higher risk of cardiovascular events compared with placebo.

- GI and CV safety: Partially selective NSAIDs
 - GI safety: Meloxicam was generally associated with no advantage in GI protection relative to other NSAIDs; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac
 - CV safety: No increased risk associated with meloxicam relative to non-selective NSAIDs; no evidence for nabumetone and etodolac
- GI and CV safety: Non-selective NSAIDs
 - No clear difference in GI safety among non-selective NSAIDs at commonly used doses.
- GI and CV safety: Aspirin
 - Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in long-term prophylactic doses.
 - There is insufficient evidence to assess the balance of GI and CV safety of aspirin in therapeutic doses compared with non-aspirin NSAIDs.
- GI and CV safety: Salsalate
 - The GI and CV safety of salsalate are not known.
 - Salsalate was associated with a lower risk of adverse events as defined using broad composite endpoints in older, flawed observational studies of patients with rheumatoid arthritis.
- Mortality
 - Individual trials were not large enough to detect differences in mortality.
 - One meta-analysis of celecoxib found no difference between celecoxib and non-selective NSAIDs, but there were few events.
 - In one fair-quality cohort study, nabumetone was associated with a lower risk of all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
- Hypertension, congestive heart failure (CHF), edema, and renal function
 - All NSAIDs and Cox-2 inhibitors can cause or aggravate these conditions.
 - There is good evidence from short-term trials that, on average, non-selective NSAIDs raised mean blood pressure by an average of about 5.0 mm Hg (95% CI, 95% CI 1.2 to 8.7). However, averages do not necessarily correspond with the likelihood of an event requiring withdrawal, medication change, or other clinical consequences.
 - There was weak evidence that aspirin and sulindac have less hypertensive effect than other nonselective NSAIDs.
 - There were no clear differences among other selective or non-selective NSAIDs for these adverse events.
 - The available evidence, while not conclusive, does not support a difference among the coxibs in the likelihood of causing hypertension, CHF, edema, or renal dysfunction.
- Hepatotoxicity
 - Clinically significant hepatotoxicity was rare.
 - Among currently marketed NSAIDs, only diclofenac was associated with a significantly higher rate of liver-related discontinuations compared with placebo (1 additional case for every 53 patients)

- Tolerability
 - Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were found to be more or similarly tolerable and aspirin and salsalate were less tolerable.
 - There were no clear differences among coxibs or among NSAIDs.
- Acetaminophen
 - Acetaminophen was modestly inferior to NSAIDs for pain and function in four systematic reviews.
 - Compared with NSAIDs, acetaminophen had fewer GI side effects (clinical trials data) and serious GI complications (observational studies).
 - Acetaminophen was not associated with an increased risk of hepatotoxicity at therapeutic doses compared to non-use.
- Glucosamine and chondroitin
 - Glucosamine found to be superior to oral NSAIDs and placebo in trials, but results may not be applicable to the U.S. because they primarily evaluated pharmaceutical grade glucosamine available in Europe.
 - Chondroitin was superior to placebo in flawed studies.

Effect of dosage and duration of treatment on the benefits and harms of oral medication use

- We found no studies of the GI or CV safety of alternative dosage strategies.
- The risk of GI bleeding increases with higher doses of non-selective NSAIDs.
- The CV risk of celecoxib was dose-dependent in a long-term prevention trial.
- The CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial.

Balance of evidence and harms

Each of the analgesics evaluated in this report was associated with a unique set of benefits and risks. Each was also associated with gaps in the evidence that would be needed to determine the true balance of benefits versus harms. The role of selective and non-selective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others, which is not surprising given the complex trade-offs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (cardiovascular, renal, GI, and others) involved.

Individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of an increase in cardiovascular risk, for example, could be an acceptable trade-off for some patients. Others may consider even a marginal increase in risk unacceptable. Factors that should be considered when weighing the potential effects of an analgesic include age (older age being associated with increased risks for bleeding and cardiovascular events), co-morbid conditions, and concomitant medication use (such as aspirin and acetaminophen). As in other medical decisions, choosing the optimal analgesic for an individual with osteoarthritis should always involve careful consideration and thorough discussion of the relevant trade-offs.

Differences in demographic and clinical subgroups

- No clear differences in safety or efficacy among different age, gender, or racial groups have been demonstrated for selective or non-selective NSAIDs.
- Among patients who had a recent episode of upper GI bleeding, there is good evidence that rates of recurrent ulcer bleeding are high (around 5% after six months) in patients prescribed celecoxib or a non-selective NSAID plus a PPI.

Concomitant anticoagulant or aspirin use

- The risk of GI bleeding when low-dose aspirin is used with a coxib is similar to the risk associated with the use of a non-selective NSAID.
- Concomitant use of anticoagulants and any non-selective NSAID increases the risk of GI bleeding three- to six-fold compared to anticoagulants alone.
- Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies.
- Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in both patients on celecoxib and those on non-selective NSAIDs in one meta-analysis.
- Rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone (7%).
- Effects of concomitant aspirin on CV risk associated with NSAIDs are unclear.

Comparison of gastrointestinal harms of NSAID reduced by co-prescribing of H2-antagonists, misoprostol, or PPIs

- Consistent evidence from good-quality systematic reviews and numerous clinical trials found PPIs to be associated with the lowest rates of endoscopically detected *duodenal* ulcers.
- Misoprostol is associated with similar rates of endoscopically detected *gastric* ulcers as PPIs.
- While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of perforation, obstruction, or bleeding, there is a high rate of withdrawals due to adverse GI symptoms.

Comparison of treatment of osteoarthritis with oral medications with topical preparations

- **Topical NSAIDs: efficacy**
 - Topical NSAIDs were similar to oral NSAIDs for efficacy, with topical diclofenac best studied.
 - Topical ibuprofen was superior to placebo in several trials.
- **Topical NSAIDs: safety**
 - Consistent evidence from good-quality trials, systematic reviews and observational studies found topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs.
 - Total adverse events and withdrawal due to adverse events were similar.
 - Data from one good-quality trial found topical NSAIDs were superior for GI events, including severe events, and changes in hemoglobin.
- **Topical salicylates and capsaicin**

- High and fair-quality, placebo-controlled trials found topical salicylates were no better than placebo.
- Topical capsaicin found to be superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

Remaining Issues

- Nearly all of the clinical trials reviewed in this report were “efficacy” trials conducted in ideal settings and selected populations. “Pragmatic” and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- The cardiovascular safety of non-selective NSAIDs has not been adequately assessed in large, long-term clinical trials. Trials comparing different non-selective NSAIDs and placebo are important to clarify the increased risk for cardiovascular events observed in some observational studies (and in an as-yet unpublished systematic review). Naproxen in particular may have a different cardiovascular safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials. The cardiovascular risks associated with the partially selective NSAIDs meloxicam, nabumetone, and diclofenac also have not been well studied.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have generally focused on assessing single adverse events. Observational studies that take a broader view of all serious adverse events would be substantially more helpful for assessing the overall trade-offs between benefits and harms.
- The cardiovascular risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new COX-2 selective analgesic.
- Meta-analyses of the risks associated with selective COX-2 inhibitors need to better assess for the effects of dose and duration, as most of the cardiovascular risks have only occurred with prolonged use and at higher doses.
- Large, long-term trials of the GI and cardiovascular safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- Given the large number of patients who meet criteria for aspirin prophylaxis for cardiovascular events, more trials comparing the effects of low-dose aspirin on the GI benefits and on CV safety are needed.
- Trials and observational studies evaluating comparative safety or efficacy should be sufficiently inclusive to evaluate whether effects differ by race or gender.

- Genetic testing could theoretically help predict patients who are at higher risk of cardiovascular complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This is a promising area of future research.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies.
- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the U.S. and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations to oral NSAIDs are needed, as these are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine.
- High-quality trials of chondroitin are lacking.
- No topical NSAIDs are FDA-approved in the U.S., yet compounding of NSAIDs is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO. A UK trial of topical versus oral ibuprofen is currently in progress and will help clarify the benefits and safety of topical versus oral NSAIDs. However, cohort studies using large observational databases may be required to adequately assess cardiovascular risk.

Table A. Summary of findings with strength of evidence

Key Question	Level of Evidence	Conclusion
1a. What is the evidence for benefits and harms of treating osteoarthritis with oral medication(s)?		
Efficacy: Non-selective NSAID vs. non-selective NSAID	Non-selective NSAID vs. non-selective NSAID: <i>good</i> . Consistent evidence from several good-quality systematic reviews and published trials. Salsalate vs. aspirin. <i>Poor</i> . One short-term trial. Salsalate or aspirin vs. non-aspirin NSAIDs. <i>Poor</i> .	No difference in efficacy between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac). No difference between salsalate and aspirin in one short-term trial. There were no trials or eligible observational studies of salsalate or aspirin vs. non-aspirin NSAIDs.
Efficacy: COX-2 selective vs. non-selective NSAID	Good. Consistent evidence from many published trials	No difference.

Efficacy: COX-2 selective vs. COX-2 selective	Good. Consistent evidence from six published trials.	No clinically significant differences at comparable doses.
GI and CV safety: Rofecoxib	Good. One large published trial, multiple meta-analyses and systematic reviews of published and unpublished trials, multiple observational studies.	In the only large, long-term trial, rofecoxib at 50 mg daily significantly reduced symptomatic ulcers and serious ulcer complications compared with naproxen in patients with RA. For rofecoxib there was 1 fewer symptomatic ulcer for every 62 patients treated; one fewer serious GI complication for every 191; and one additional MI for every 333 patients. The overall rate of serious adverse events was higher with rofecoxib 50 mg than naproxen. A good-quality systematic review, observational studies, and results of a polyp prevention trial are consistent with these findings.
GI and CV safety: Celecoxib	Fair: Multiple meta-analyses and systematic reviews of mostly short-term published and unpublished trials, multiple observational studies.	In the only published large, long-term trial, celecoxib was no different than diclofenac or ibuprofen for complicated or symptomatic ulcers at the end of the trial. In subgroup analyses of patients not on aspirin, celecoxib was superior to ibuprofen but not to diclofenac for ulcer complications. There was no increase in the rate of cardiovascular events, though analyses were performed on truncated 6-month data. The overall rate of serious adverse events was similar to ibuprofen and diclofenac. Systematic reviews and other meta-analyses of primarily short-term, unpublished data and lower doses found that celecoxib was superior to non-selective NSAIDs for ulcer complications. Observational studies are generally consistent with the short-term trials. However, a long-term polyp prevention trial found an increased, dose-dependent risk of myocardial infarction with celecoxib compared with placebo.
GI and CV safety: Valdecoxib	Fair: Fair quality meta-analyses of published and	Valdecoxib was associated with a lower short-term risk of upper GI

	unpublished trials	complications compared with non-selective NSAIDs. There was one fewer upper GI complication with valdecoxib for every 78 patients treated for 3 to 6 months. There was no association between valdecoxib and myocardial infarction in primarily short-term chronic pain trials. However, two short-term trials in a high-risk post-coronary artery surgery setting found that valdecoxib was associated with a two- to three-fold higher risk of cardiovascular events compared with placebo.
GI and CV safety: Partially selective NSAIDs	<p>GI safety: Fair for meloxicam (short-term RCTs, meta-analyses, observational studies); poor for nabumetone and etodolac</p> <p>CV safety: Poor for all; two observational studies for meloxicam</p>	<p>GI safety: Meloxicam had no advantage in GI risk relative to other NSAIDs; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac</p> <p>CV safety: No increased risk associated with meloxicam relative to non-selective NSAIDs; no evidence for nabumetone and etodolac</p>
GI and CV safety: Non-selective NSAIDs	<p>Good for GI safety. Consistent evidence from many published trials, systematic reviews, and observational studies</p> <p>Fair for CV safety. No large, long-term controlled trials. Almost all evidence from observational studies</p>	<p>No clear difference in GI safety between non-selective NSAIDs at commonly used doses. Naproxen was associated with a modest cardiovascular protective effect compared with other NSAIDs in a good-quality systematic review of observational studies, but methodological issues could have affected the results.</p> <p>CV safety of other non-aspirin NSAIDs is not clear. A large systematic review of RCTs addressing this issue has not yet been published.</p>
GI and CV safety: Aspirin	Fair. Many trials and systematic reviews, but almost exclusively in patients receiving aspirin for cardiovascular prophylaxis.	Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in prophylactic doses. Insufficient evidence to assess safety of aspirin in therapeutic doses compared with non-aspirin NSAIDs.
GI and CV safety: Salsalate	Poor. Almost all data are	Salsalate was associated with a lower

	from fair-to-poor quality observational studies in patients with rheumatoid arthritis.	risk of adverse events as defined using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs. Almost no data is available on CV safety.
Mortality	Fair. Individual trials not large enough to detect differences in mortality. One meta-analysis of celecoxib using unpublished information, and one fair-quality observational study of non-selective NSAIDs.	No difference between celecoxib and non-selective NSAIDs, but few events. In one cohort study, nabumetone was associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, edema, and renal function	Fair. Multiple systematic reviews, clinical trials, and observational studies, but analyses limited by inconsistent reporting of results and probable publication bias	One major trials and several observational studies suggest increased risks for heart failure with rofecoxib, but these are not conclusive. Rofecoxib also associated with more cardiorenal events than celecoxib in three head-to-head trials of high-risk patients, but nonequivalent dosing limits interpretation of these results. No clear differences between celecoxib, partially selective, and non-selective NSAIDs.
Hepatotoxicity	Good. Systematic reviews of multiple trials and observational studies	Clinically significant hepatotoxicity was rare. Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. Among currently marketed NSAIDs, diclofenac was associated with a higher rate of liver-related discontinuations compared with placebo (2.17%).
Tolerability	Good for coxibs and non-selective NSAIDs (consistent results from multiple systematic reviews); fair for partially selective NSAIDs and aspirin (few meta-analyses and short-term trials)	Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were at least as well tolerated and aspirin was less tolerated; no differences among coxibs or among non-selective NSAIDs
Acetaminophen	Good overall. Consistent results from multiple systematic reviews for	Acetaminophen is modestly inferior to NSAIDs for pain and function. Acetaminophen is superior to NSAIDs

	efficacy and GI adverse events. Poor for cardiovascular safety (no evidence) and fair for renal safety (observational studies)	for GI side effects (clinical trials data) and GI complications (observational studies). Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). Acetaminophen is not associated with an increased risk of hepatotoxicity at therapeutic doses.
Glucosamine and chondroitin	Fair. Inconsistent evidence from clinical trials. Most promising results have been obtained in trials funded by a European manufacturer of pharmaceutical grade glucosamine not approved in the U.S.	Glucosamine was superior to oral NSAIDs and placebo in trials evaluating pharmaceutical grade glucosamine and funded by its manufacturer. Other trials found no difference between glucosamine and placebo or glucosamine and oral NSAIDs. Final results of an NIH funded trial in the U.S. are pending. Chondroitin was superior to placebo, but trials were flawed.
1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	Good for safety (consistent evidence from multiple clinical trials and observational studies), no evidence for alternative dosage strategies.	Risk of GI bleeding increases with higher doses of non-selective NSAIDs. Effects of dose and duration are somewhat inconsistent. Celecoxib was most effective for GI safety at 6 months and not after longer follow-up in the CLASS trials. Dose-dependent CV risk of celecoxib has been observed in a long-term prevention trial. CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial. Most, but not all, observational studies suggest a dose-dependent effect of rofecoxib on MI risk.
Key Question 2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Good (age, sex) Poor (race)	Most studies included a majority of women. The risks of GI and CV events increase in older patients. The data that selective COX-2 inhibitors are safe and

		efficacious in different racial groups have been presented to the FDA, but no clear differences have been described in the peer-reviewed literature.
Pre-existing disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Previous bleeding: Good Hypertension, edema: Fair Ischemic Heart Disease: Poor (no comparative studies) Heart failure: Fair	Risk of bleeding is higher in patients with prior bleeding or PUD. Two trials found high rates of recurrent ulcer bleeding in patients randomized to celecoxib versus a non-selective NSAID + PPI. Risk of CV and renal events is higher in patients with cardiac and renal co-morbidities. In a single observational study that examined mortality, rofecoxib and non-selective NSAIDs were associated with higher rates of death and recurrent heart failure than celecoxib.
Concomitant anticoagulant use	Fair overall: Primarily observational studies	Concomitant use of anticoagulants and non-selective NSAIDs increase the risk of GI bleeding three- to six-fold. Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies. Warfarin plus aspirin (prophylactic doses) increased risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.
Concomitant aspirin use	Good for GI safety: Consistent evidence from clinical trials and observational studies Fair for CV safety: Subgroup analyses from few trials, few observational studies	Concomitant use of aspirin attenuates or eliminates the GI benefits of selective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on non-selective NSAIDs in one meta-analysis. In one trial, rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone

		(7%). Effects of concomitant aspirin on CV risk associated with NSAIDs are unclear.
3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or PPIs?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Misoprostol and PPIs offer some advantages over double-dose H2-antagonists. PPIs are associated with the lowest rates of endoscopically detected <i>duodenal</i> ulcers. Misoprostol is associated with similar rates of endoscopically detected <i>gastric</i> ulcers as PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of clinical GI events, this clinical advantage is accompanied by an increased risk of GI-related adverse event withdrawals.
4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?		
Topical NSAIDs: efficacy	Good: Consistent evidence for selected topical NSAIDs from clinical trials	Topical NSAIDs are similar to oral NSAIDs for efficacy. Topical diclofenac is the best studied, though many trials evaluated a formulation using a DMSO carrier that is not available in the U.S. Topical ibuprofen was superior to placebo in several trials.
Topical NSAIDs: safety	Good: Consistent evidence from trials and systematic reviews and observational studies	Topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events are similar. Topical NSAIDs are superior for GI events, including severe events, and changes in hemoglobin (data from one good-quality trial).
Topical salicylates: (including capsaicin)	Fair: Only placebo-controlled trials, many of which were flawed	Topical salicylates were no better than placebo in higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

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Chapter 1. Introduction

Osteoarthritis, the most common form of arthritis, is associated with substantial disability and reduced quality of life.¹ Among U.S. adults aged 30 or older, approximately 6% have symptomatic osteoarthritis of the knee, and 3% have symptomatic osteoarthritis of the hip.² Osteoarthritis increases with age, with the incidence and prevalence increasing 2- to 10-fold from age 30 to 65, and continues to increase after age 65.³ Osteoarthritis accounts for more disability in walking, stair climbing, and other tasks requiring use of the lower extremities than any other disease, particularly in the elderly.⁴ The total costs for arthritis, including osteoarthritis, may be greater than 2% of the gross domestic product,² with more than half of these costs related to work loss.⁴

In addition to non-pharmacologic interventions (such as physical therapy, weight reduction, and exercise), numerous medications and over-the-counter supplements are available to treat pain and potentially improve functional status in patients with osteoarthritis. Each class of medication or supplement is associated with a unique balance of risks and benefits. In addition, efficacy and safety may also vary for individual drugs within a class. Oral medications commonly used to treat osteoarthritis include nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. Commonly used over-the-counter supplements include glucosamine and chondroitin. Topical agents frequently used by patients with osteoarthritis are rubefacients (including capsaicin), NSAIDs, and miscellaneous preparations.⁵ Opioid medications are also frequently used for patients with chronic pain, especially if it is refractory to other therapies, but are usually not recommended for first-line treatment for osteoarthritis or other conditions because of risks of addiction, tolerance, diversion, and other adverse events.^{6, 7}

NSAIDs exert analgesic, anti-inflammatory, and anti-pyretic effects by blocking *cyclo-oxygenases* (COX), enzymes that are needed to produce *prostaglandins*. COX-1 and COX-2 are different kinds of cyclo-oxygenases. COX-2, found in joint and muscle, contributes to pain and inflammation. Because they block COX-2, non-steroidal anti-inflammatory drugs reduce pain significantly in patients with arthritis,⁸ low back pain,⁹ minor injuries, and soft tissue rheumatism compared with placebo.

NSAIDs, however, are also associated with important adverse effects. NSAIDs cause gastrointestinal (GI) bleeding because they also block the COX-1 enzyme, which protects the lining of the stomach from acid. In the 1990s in the United States, nonaspirin NSAIDs are estimated annually to have caused 32,000 hospitalizations and 3,200 deaths from GI bleeding.¹⁰ A risk analysis¹¹ based on a retrospective case-control survey of emergency admissions for upper GI disease in two United Kingdom general hospitals provided useful estimates of the frequency of serious GI complications from NSAIDs.¹² In people taking NSAIDs, the 1-year risk of serious GI bleeding ranges from 1 in 2,100 in adults under age 45 to 1 in 110 for adults over age 75, and the risk of death ranges from 1 in 12,353 to 1 in 647 (Table 1). In addition to age, prednisone use, disability level, and previous NSAID-induced GI symptoms are risk factors for GI bleeding.

Table 1. One year risk of GI bleeding due to NSAID

Age range (years)	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAID
<i>Risk in any one year is 1 in:</i>		
16-45	2100	12,353
45-64	646	3800
65-74	570	3353
≥ 75	110	647

Data are from Blower, ¹² recalculated in Moore ¹¹ and in Bandalier ¹³
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NSAIDs differ in their selectivity for COX-2—how much they affect COX-2 relative to COX-1. Theoretically, an NSAID that blocks COX-2 but not COX-1 might reduce pain and inflammation in joints but leave the stomach lining alone. Appendix A¹⁴ summarizes the NSAIDs and their selectivity based on assay studies (done in the laboratory instead of in living patients). The table gives an idea of how widely NSAIDs vary in their selectivity, but should be interpreted with caution. Different assay methods give different results, and no assay method can predict what will happen when the drug is given to patients. Clinical studies, rather than these assay studies, are the best way to determine whether patients actually benefit from using more selective NSAIDs.

In addition to their propensity to cause GI bleeding, NSAIDs are also associated with adverse effects on blood pressure, renal function, and fluid retention. Mechanisms may involve attenuation of prostaglandin-mediated vasodilation, promotion of sodium and water retention, increased vascular resistance, and increased renal endothelin-1 synthesis.¹⁵⁻¹⁷

An association between selective COX-2 inhibitors and increased rates of myocardial infarction was first observed in the large Vioxx Gastrointestinal Outcomes Research (VIGOR) trial.¹⁸ The increase in thromboembolic cardiovascular event risk is thought to be related to suppression of endothelial-derived prostaglandin I₂ formation by selective COX-2 inhibition, in the setting of unaffected platelet production of pro-thrombotic COX-1 mediated thromboxane A₂.¹⁹ On September 30, 2004, rofecoxib was withdrawn from the market after a trial of polyp prevention found an increased risk of myocardial infarction compared with placebo.²⁰ On December 9, 2004, the US Food and Drug Administration issued a black-box warning for valdecoxib for life-threatening skin reactions and increased cardiovascular risk. This drug was also subsequently withdrawn.²¹

Aspirin, or acetylsalicylic acid, has long been known to have analgesic, anti-pyretic, and anti-inflammatory effects.²² It is thought to be the most consumed medicinal drug in the world. Like the non-aspirin NSAIDs, aspirin's effects are due to blockade of cyclo-oxygenases. However, an important distinction between aspirin and non-aspirin NSAIDs is that aspirin also induces long-lasting functional defects in platelets (although non-aspirin NSAIDs also have shorter-lived effects on platelet aggregation). Because of its antiplatelet effects, aspirin is also used prophylactically to reduce the risk of thrombotic events.²³ Salsalate, a nonacetylated salicylate, is a prodrug of salicylic acid, the active metabolite of aspirin. However, salsalate is considered a relatively weak inhibitor of cyclo-oxygenases.²⁴

Acetaminophen (also known as paracetamol) is an anti-pyretic and analgesic medication that is not thought to have significant anti-inflammatory properties. Although its mechanism of inducing analgesia is still not completely understood, it is thought to work in part by indirectly decreasing production of prostaglandins through inhibitory effects involving COX-2.^{15, 25} Acetaminophen is frequently recommended as a first line agent for osteoarthritis and other pain conditions because of its perceived favorable safety profile—particularly with regard to ulcer risk.²⁶

Chondroitin sulfate and glucosamine sulfate are natural compounds found in cartilage. Both are marketed to patients who have osteoarthritis. The precise mechanisms of action are unknown, but may involve promoting maintenance and repair of cartilage. Glucosamine, for example, has been shown to increase proteoglycan synthesis.²⁷ In the European Union countries, glucosamine is available as a prescription drug manufactured by the Rotta Pharmaceutical Company. In the U.S., by contrast, glucosamine and chondroitin are considered dietary

supplements and are not regulated as pharmaceuticals. Adequate standardization of glucosamine and chondroitin preparations is a significant concern, as it has been shown that the actual content often varies substantially from what is stated on the label.²⁸

Topical administration of NSAIDs could theoretically result in local analgesic and anti-inflammatory effects by direct absorption through the skin, with reduced systemic adverse events compared with oral administration.²⁹ Experimental studies indicate that topical administration is associated with substantially higher concentrations of NSAIDs in soft tissue (particularly meniscus and cartilage) and lower peak plasma concentrations compared with oral administration.⁵ For a topical NSAID to be effective, it has to reach the inflamed tissue in sufficient concentrations to produce analgesic and anti-inflammatory activity. The solubility of specific NSAIDs varies considerably, and is also affected by the carrier or formulation used.²⁹ Superior *in vivo* permeability characteristics, however, may not predict clinical effectiveness.

In contrast to topical NSAIDs, whose mechanism of action involves inhibition of cyclooxygenase, topical rubefacients are thought to relieve pain through counter irritation.^{5, 30} Although the mechanism of action of topical preparations containing salicylate esters is unclear, they are now usually classified as rubefacients rather than topical NSAIDs because they may not work via inhibition of cyclo-oxygenase.^{5, 31} Capsaicin, which is also often classified as a rubefacient, is derived from the hot chili pepper (*Capsicum* species). It is applied topically and thought to work by stimulating the release of substance P and other neuropeptides from sensory nerve endings.³² Although this release can initially lead to burning and pain, analgesia occurs after repeated and continued application, as substance P becomes depleted. Although a wide variety of other rubefacients are available, only topical salicylates and capsaicin were included in this review.

The purpose of this report was to assess the comparative efficacy and safety of non-opioid oral medications (selective and non-selective non-aspirin NSAIDs, aspirin, salsalate, and acetaminophen), over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) for osteoarthritis.

Scope and Key Questions

1. What is the evidence for benefits and harms of treating osteoarthritis with oral medication(s)? How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use? (*Note: This question addresses the therapeutic benefits of long-term use for the condition osteoarthritis. However, the question does address all harms associated with NSAID use, including use for other labeled indications such as the treatment of rheumatoid arthritis.*)

Oral NSAIDs include:

- aspirin
- celecoxib
- choline magnesium trisalicylate
- diclofenac
- diflunisal
- etodolac
- fenoprofen
- mefenamic acid
- meloxicam
- nabumetone
- naproxen
- oxaprozin
- piroxicam
- rofecoxib

- flurbiprofen
- ibuprofen
- indomethacin
- ketoprofen
- ketoprofen ER
- ketorolac
- meclofenamate sodium
- salsalate
- sulindac
- tenoxicam*
- tiaprofenic acid*
- tolmetin
- valdecoxib

* These drugs are currently not approved for use in the United States by the FDA.

Other oral medications include acetaminophen, chondroitin, and glucosamine. See Appendix A for a more detailed listing of these drugs, included dosing information and indications.

For this report, we defined the terms “selective NSAID” or “COX-2 selective NSAID” as drugs in the “coxib” class (celecoxib, rofecoxib, and valdecoxib). We defined “partially selective NSAIDs” as other drugs shown to have in vitro COX-2 selectivity (etodolac, nabumetone, meloxicam). The salicylic acid derivatives aspirin and salsalate were also considered a separate subgroup. We defined “non-aspirin, non-selective NSAIDs” or simply “non-selective NSAIDs” as all other NSAIDs.

“Benefits” include relief of pain and osteoarthritic symptoms and improved functional status. The main outcome measures for this review were pain, functional status, and discontinuations due to lack of efficacy. Frequently used outcome measures include visual and categorical pain scales.³³

Visual analogue scale (VAS): Patients indicate their level of pain, function, or other outcome by marking a scale labeled with numbers (such as 0 to 100) or descriptions (such as “none” to “worst pain I’ve ever had”). An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient’s subjective experience of pain. This poses a challenge in objectively comparing different patients’ scores, or even different scores from the same patient.

Categorical pain scales consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose among categories that may not accurately describe their pain. A variety of disease-specific and non-specific scales are used to assess these outcomes in patients with osteoarthritis. Commonly used categorical pain scales include:

- The *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) is a 24-item, disease-specific questionnaire used to assess the functional status of patients with osteoarthritis of the knee and hip. A lower score indicates better function.³⁴
- The *Medical Outcomes Short Form-36 (SF-36)* health survey is a commonly used general instrument for measuring health-related quality of life across different diseases.³⁵
- *Patient Global Assessment of Disease Status* and *Investigator Global Assessment of Disease Status*. The patient or investigator answers questions about the overall response to treatment, functional status, and pain response, using a VAS or Likert scale.
- *American College of Rheumatology (ACR) criteria* measure disease activity and response to treatment. ACR 20, ACR 50, or ACR 70 reflect either an improvement to the 20%, 50%, or 70% level in the parameters outlined.

Another method for measuring outcomes is classifying patients dichotomously as “responders” or “non-responders.” Responders are often defined as patients with at least a 50%

improvement in pain or function. The *Outcomes Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria*, for example, were developed through a consensus process and classifies patients as responders if they meet specific pre-defined criteria ($\geq 50\%$ improvement in pain or function that was ≥ 20 mm on a 100 mm VAS, or a $\geq 20\%$ improvement in at least two of pain, function, or patient global assessment that was ≥ 10 mm on a 100 mm VAS).³⁶

“Harms” include tolerability; cardio-, hepato-, renal, and gastrointestinal toxicity; and increased risk for hospitalizations, drug interactions, and death. For gastrointestinal toxicity, we focused on serious complications associated with NSAIDs including perforation, bleeding ulcer, and gastric outlet obstruction, though we also evaluated other gastrointestinal side effects (such as nausea, dyspepsia, and gastrointestinal tolerability). We only considered rates of endoscopic ulcers when data on clinical ulcer complications were not available.

2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?

- Demographic subgroups include age, sex, and race.
- Co-existing diseases include hypertension, edema, ischemic heart disease, heart failure, PUD, and history of previous bleeding due to NSAIDs.
- Concomitant medication use includes anticoagulants and aspirin.

3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors?

4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?

Topical preparations include:

- capsaicin
- diclofenac
- ibuprofen
- ketoprofen
- salicylate

Chapter 2. Methods

Topic Development

The topic for this report was nominated in a public process. The key questions were developed by investigators from the Oregon EPC with input from a Technical Expert Panel (TEP) formed for this project. Contacted via teleconference, the TEP served in an advisory capacity for this report, helping to refine key questions, identify important issues, and define parameters for the review of evidence.

Search Strategy

A comprehensive search of the scientific literature was conducted to identify relevant studies addressing the key questions. Results from previously conducted meta-analyses and systematic reviews on these topics were sought and used where appropriate and updated when necessary. To identify systematic reviews, in addition to MEDLINE, we searched the Cochrane Database of Systematic Reviews and the websites of the Canadian Coordinating Office for Health Technology Assessment (CCOHTA), Bandolier, and the NHA Health Technology Assessment Programme.

To identify articles relevant to each key question, we searched the Cochrane Database of Systematic Reviews (through 3rd Quarter 2005) the Cochrane Central Register of Controlled Trials (through 3rd Quarter 2005) and Ovid ®MEDLINE (1966- July, 2005.) We used relatively broad searches, combining terms for drug names with terms for relevant research designs, limiting to those studies that focused on osteoarthritis and rheumatoid arthritis (see Appendix B for the complete search strategy). Other sources include reference lists of review articles and unpublished materials from the US Food and Drug Administration (FDA.) Pharmaceutical manufacturers were invited to submit scientific information packets, including citations if applicable. All 2,665 citations from these sources were imported into an electronic database (EndNote® 9.0) and considered for inclusion.

Study Selection

Systematic reviews and controlled trials pertinent to the key questions were considered as the highest priority for inclusion in the report. We retrieved any blinded or open, parallel or crossover randomized controlled trial that compared a COX-2 and/or NSAID to each other, another active comparator, or placebo. We included long-term cohort and case-control studies with at least 1,000 cases/participants that evaluated serious gastrointestinal and cardiovascular endpoints that were inadequately addressed by randomized controlled trials.

Data Extraction

The following data were extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), method of outcome ascertainment if available, and results for each outcome, focusing on efficacy and safety. We recorded intention-to-treat results if

available.

Quality Assessment

Assessing Research Quality

We assessed the internal validity (quality) of systematic reviews and randomized trials based on the predefined criteria listed in Appendix C. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).³⁷ We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the “fair quality” category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A “poor quality” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Assessing Research Applicability

The applicability of trials and other studies was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the sponsor.

Rating a Body of Evidence

Overall quality ratings for an individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

We assessed the overall strength of evidence for a body of literature about a particular key question, by examining the type, number and quality of studies; the strength of association; the consistency of results within and between study designs; and the possibility for publication bias. Consistent results from good-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies were true (that is, the entire body of evidence would be considered “good-quality.”) For a body of fair-quality studies, however, consistent results may indicate that similar biases are operating in all the studies. Unvalidated assessment techniques or heterogeneous reporting methods for important outcomes may weaken the overall body of evidence for that particular outcome or make it difficult to accurately estimate the true magnitude of benefit or harm. Poor-quality studies are not considered in the assessment of the overall body of evidence.

Data synthesis

Effectiveness versus Efficacy

Throughout this report, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of “effectiveness” outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales. Further discussion of these issues is available at <http://effectivehealthcare.ahrq.gov/reference/purpose.cfm>.

Data presentation

We constructed evidence tables showing study characteristics, quality ratings, and results for all included studies. We also performed two quantitative analyses for this review. An important limitation of observational studies of NSAIDs is that none simultaneously assessed the risk for serious cardiac and GI events. We re-analyzed data from a set of observational studies that reported rates of three different serious adverse events in the same population. We assumed that the adverse events occurred independently and that the logarithm of the rate ratios was distributed normally. After estimating the effect (number of events prevented or caused) for each of the three adverse events, we estimated the net effects on all three serious adverse events using Monte Carlo simulation.

We pooled clinical success rates for withdrawal due to adverse events from head-to-head trials of topical versus oral NSAIDs using a random effects model (Dersimonian-Laird method, implemented in RevMan® statistical software. We performed standard chi-square tests for heterogeneity. Because only four trials were available for pooling, we did not plan to perform meta-regression analyses for potential sources of significant ($p < 0.10$) heterogeneity.

Chapter 3. Results

Overview

Searches identified 2,665 publications: 1,516 from the Cochrane Central Register of Controlled Trials, 69 from the Cochrane Database of Systematic Reviews, 906 from MEDLINE and 173 from the combination of other sources listed above. Following application of inclusion criteria, 320 publications were included in this review.

Key Question 1a. What is the evidence for benefits and harms of treating osteoarthritis with oral medication(s)?

Benefits: Effectiveness and efficacy

Effectiveness Studies

No controlled clinical trials or studies of COX-2 inhibitors and/or NSAIDs were conducted in mainly primary care or office-based settings, used broad enrollment criteria, or used longer-term, “real-life” outcomes.

Efficacy

NSAIDs vs. NSAIDs Several good-quality systematic reviews by the Cochrane Collaboration evaluated trials that compared non-aspirin NSAIDs published through 1994 for OA of the hip,³⁸ 1998 for OA of the back,⁹ and 1997 for OA of the knee.³⁹ These reviews found no clear differences among non-aspirin and primarily non-selective NSAIDs in efficacy. There were also no differences found between diclofenac and etodolac SR in patients with OA of the knee⁴⁰ or between piroxicam and conventional etodolac in patients with OA of the knee or hip⁴¹ in two trials published subsequent to the Cochrane reviews.

Nabumetone was similar in efficacy to the non-selective NSAIDs diclofenac SR⁴² and etodolac⁴³ in two 4-week trials, as reported in the Cochrane review of OA of the knee.³⁹

No studies of meloxicam, salsalate, or aspirin were included in any Cochrane reviews. We identified nine double-blinded trials of meloxicam 7.5mg, 15mg, and 25mg versus other NSAIDs (Appendix D) and found that there were generally no differences in efficacy.⁴⁴⁻⁵² In two of the trials, however, patients taking non-selective NSAIDs were significantly less likely to withdraw due to lack of efficacy than patients taking meloxicam.^{46, 51}

In the only head-to-head trial of salsalate (3 g) in patients with OA, efficacy was similar to that of 3.6 g soluble aspirin after two weeks of treatment.⁵³

Celecoxib vs. NSAIDs Celecoxib and non-selective NSAIDs were associated with similar decreases in symptom severity and improvements in functional capacity (PGA, WOMAC) after 6- to 24-weeks in five published trials of patients with primarily OA (Appendix E).⁵⁴⁻⁵⁷

A good-quality systematic review funded by the makers of celecoxib reached similar conclusions based on combined data from published^{54, 55, 58-62} and unpublished studies^{63, 64} of at least 12 weeks' duration in patients with either OA or RA.⁶⁵

Using an alternative endpoint and the largest volume of information from company clinical

trial reports, a more recent systematic review (2005) reached slightly different conclusions about the relative efficacy of celecoxib and NSAIDs.⁶⁶ Moore et. al. meta-analyzed combined data from 31 primarily short-term (≤ 12 weeks) trials and concluded that celecoxib at dose of 200-400 mg (RR 1.1; 95% CI 1.02, 1.23) was associated with higher rates of withdrawals due to lack of efficacy than non-selective NSAIDs. The unpublished data used in this meta-analysis add value in that they may help provide the most precise estimates to-date of efficacy, and they highlight the importance of having all relevant trials available for examination. However, although the meta-analysis methods appeared appropriate, we could not adequately rate its quality because much of the data used are not available to the public. It is therefore impossible to verify whether the meta-analysis assessed validity appropriately, abstracted outcomes correctly, or otherwise confirm the reproducibility and conduct of the meta-analysis.

CLASS remains the longest-term trial at 26-52 weeks in duration and randomized a total of 7,968 patients to celecoxib, ibuprofen, or diclofenac.⁵⁷ CLASS focused on adverse effects rather than efficacy. A higher proportion of NSAID patients withdrew for lack of efficacy (14.8% vs. 12.6%, $p=0.005$), but no other efficacy results were reported.

SUCCESS-1 remains the largest trial, a 12-week, multinational, double-blind, randomized trial of 13,274 patients with osteoarthritis of the hip, knee, or hand, compared celecoxib 200 mg daily or 400 mg daily to diclofenac and naproxen. The trial is not yet published, but the authors reported in an abstract that there were no differences in pain reduction (VAS, WOMAC).⁶⁷⁻⁶⁹

Rofecoxib vs. NSAIDs We were unable to determine whether all manufacturer-sponsored trials of rofecoxib versus NSAIDs have been published. Thirteen published trials are summarized in Appendix F, where they are sorted by length of followup.^{18, 70-81} All but one of the trials included osteoarthritis patients, and all but two^{76, 78} were supported by the manufacturer of rofecoxib. All but one of the OA trials⁷⁹ have been previously analyzed in a good-quality Cochrane review.⁸² Results of the Cochrane review are consistent with our findings that there were no consistent differences between rofecoxib and non-selective NSAIDs in efficacy for OA. In addition, one large, good-quality trial indicates that rofecoxib is equivalent to non-selective NSAIDs in efficacy for rheumatoid arthritis.^{18, 83}

Valdecoxib vs. NSAIDs In clinical trials submitted to the FDA, valdecoxib was as effective as ibuprofen (800mg 3 times/day), diclofenac (75mg twice daily), and naproxen (500mg twice daily) in treating osteoarthritis symptoms. Published trials found no difference in efficacy between valdecoxib and naproxen⁸⁴⁻⁸⁶ or ibuprofen or diclofenac.⁸⁷ A fifth trial found no difference in efficacy between valdecoxib 20-40 mg and diclofenac 75 mg slow release in treating rheumatoid arthritis.⁸⁸

Selective COX-2 inhibitors vs. selective COX-2 inhibitors We found six published randomized, multicenter, fair-to-good quality trials that directly compared COX-2 inhibitors for osteoarthritis of the knee.⁸⁹⁻⁹³ Pharmaceutical manufacturers were reported as funding sources in all but one study.⁹² Three earlier studies funded by the maker of celecoxib^{89, 90, 94} found no difference in efficacy between rofecoxib 25mg and celecoxib 200mg, but found a higher rate of adverse effects with rofecoxib. Another (VACT, for *Vioxx Acetaminophen Celecoxib Trial*)⁹¹ trial, conducted by the maker of rofecoxib, found that rofecoxib 25mg was more effective than celecoxib 200mg, with no differences in rates of adverse effects. The most recent study, funded by the maker of celecoxib,⁹³ found no difference in either efficacy or adverse effects between celecoxib 200 mg and rofecoxib 25 mg (Evidence Tables 1 and 1a).

Rofecoxib 25 mg and celecoxib 200 mg had similar effects on patients' pain intensity, 3-hour pain relief, global assessment of efficacy and rescue medication use in a fair-quality, 7-day study

of 30 patients with osteoarthritis of the knee.⁹² Three larger trials appeared to enroll patients with similar demographics and baseline levels of pain (see table below).^{91, 93, 95} All compared rofecoxib 25mg qd and celecoxib 200mg qd in patients with flare-ups of chronic osteoarthritis of the knee. All were 6-week trials.

Table 2. Comparison of rofecoxib and celecoxib in flare-ups of chronic osteoarthritis of the knee

Characteristic	McKenna ⁹⁵	Geba ⁹¹	Gibofsky ⁹³
Rofecoxib 25mg (n)	59	95	190
Celecoxib 200mg (n)	60	97	189
Aspirin 325 qd permitted	Yes	No	Yes
Mean age	62	62.6	62.9
Mean osteoarthritis duration	10.5 years	10 years	9 years
Percent white	80%	85%	NR
Baseline pain on walking (score)	72	72	68
Discontinued trial by 6 wks:			
Rofecoxib 25mg	16%	19%	15%
Celecoxib 200mg	22%	17%	16%

All were probably adequately randomized and blinded, and didn't have statistically significant differences in baseline characteristics. However, there were some discrepancies in McKenna and Geba. In McKenna, the proportion of patients with a past history of ulcers was higher for celecoxib (10% vs. 5%), and the proportion that had a past history of nonspecific GI symptoms was higher for rofecoxib (38% vs. 46%). The proportion of white patients was the same in the celecoxib and rofecoxib groups (84% vs. 85%), but was lower in the placebo group (73%). In Geba, the rofecoxib 25mg group had a higher proportion of women (72.6% vs. 64.9%) and a lower proportion of white subjects (82.1% vs. 87.6%) than the celecoxib 200mg group. The main article did not report the baseline WOMAC and global assessment scores of patients in the different treatment groups; a response to a letter to the editor states that the baseline WOMAC scores were similar.

More recently, Gibofsky and colleagues hypothesized that perhaps neither McKenna nor Geba were powered sufficiently to measure differences between celecoxib and rofecoxib. Gibofsky described the McKenna study as being powered only to compare active treatments with placebo and the Geba study as powered to compare rofecoxib with acetaminophen. Therefore, Gibofsky, along with some authors of the McKenna study, set out to conduct a study powered to compare celecoxib and rofecoxib, with a sample size based on results of the McKenna study.

Efficacy results are summarized in Table 3 below. Mean change in WOMAC VAS score for pain on walking was similar for celecoxib 200 mg and rofecoxib 25 mg across studies. Compared with celecoxib on other VAS scores reported in Geba, rofecoxib had significantly larger mean reductions in Rest Pain and Night Pain and a similar mean reduction in Morning Stiffness. Similar mean VAS reductions in Arthritis Pain were seen for celecoxib and rofecoxib in McKenna. WOMAC Composite Score results from Geba and Gibofsky are conflicting.

Table 3. Head to head efficacy comparisons at 6 weeks (mean change from baseline)

	WOMAC VAS Scores					WOMAC Composite Subscales			
	Walking pain	Rest pain	Morning stiffness	Night pain	Arthritis pain	Pain	Stiffness	Function	Total
Geba ⁹¹									
Rofecoxib	-42	-31.1*	-36.2	-32.7**	nr	-35.4*	-35*	-29.7	-26
Celecoxib	-36.2	-23.4	-29.1	-22.6	nr	-28.6	-27.9	-24.9	-26

McKenna⁹⁵

Rofecoxib	-38	nr	nr	nr	-40	nr	nr	nr	nr
Celecoxib	-38	nr	nr	nr	-39	nr	nr	nr	nr

Gibofsky⁹³

Rofecoxib	-29.2	nr	nr	nr	nr	-42.6	-34.7	-35.5	-20.1
Celecoxib	-31.5	nr	nr	nr	nr	-42.0	-36.7	-37.9	-22.1

*p≤0.05

**p<0.001

Geba and his colleagues noted that, regarding the WOMAC scores, "There is no current consensus on the magnitude of effects that is clinically important." A 1992 consensus conference found that a difference of 15 to 20 points on a VAS for pain and global disease activity was "clinically significant," but this has never been validated in clinical studies.⁹⁶ A more recent analysis of data from randomized trials estimated that the minimal perceptible improvement for each WOMAC scale was 11 mm.⁹⁷ In the Geba trial, WOMAC scores differed by eight points or less between celecoxib 200mg and rofecoxib 25mg.

Safety: significant gastrointestinal and cardiovascular events

Rofecoxib and celecoxib: GI and CV safety in CLASS and VIGOR

GI safety. Two pivotal studies were large enough to evaluate serious complications of peptic ulcer disease (bleeding, perforations, obstruction) as a primary endpoint in average-risk patients (those without a recent UGI bleed). The VIGOR trial¹⁸ evaluated rofecoxib versus naproxen and the CLASS trials⁵⁷ evaluated celecoxib versus ibuprofen and diclofenac..

VIGOR (Vioxx Gastrointestinal Outcomes Research) Trial. VIGOR, a randomized, double-blind trial, compared twice the highest recommended dose of rofecoxib (50 mg daily) to naproxen 500 mg twice a day in 8,076 patients with rheumatoid arthritis. VIGOR found a statistically significant reduction in complicated upper GI events (defined as perforation, obstruction, or severe upper gastrointestinal bleeding; see Appendix G. During a median follow-up of 9 months, the rates of confirmed upper gastrointestinal events were 3.0% vs. 1.4% (NNT to prevent one event 62), and the rates of complicated, confirmed upper gastrointestinal events were 0.9% vs. 0.4% (NNT 192).

VIGOR met all but one of the criteria for a good-quality study. The one weakness was the number of subjects who had incomplete followup. VIGOR was designed to be a 13-month study, but half of the patients were followed for 9 months or less, and only about 1,000 patients (13%) were followed for longer than 10 months. By 13 months, about 29% of the subjects had discontinued the study drugs. Similar proportions discontinued naproxen or rofecoxib because of an adverse event (naproxen—16.1%, rofecoxib—16.4%).

In 2003, the VIGOR investigators published a *post hoc* analysis of lower GI events, defined as bleeding with a 2 g/dL drop in hemoglobin or hospitalization, or hospitalization for perforation, ulceration, diverticulitis, or obstruction.⁹⁸ There were 11 events in the rofecoxib group (0.41 per 100 patient-years) and 24 events in the naproxen group (0.41 versus 0.89 per 100 patient-years; RR 0.46, 95% CI 0.22 to 0.93). The absolute risk difference (per 100 patient-years) was -0.48 (95% CI -0.91 to -0.05), with a NNT of 208. When the investigators combined the analysis of lower GI events with the previously reported results on upper GI complications, the rates of all serious GI events were 0.96 for rofecoxib and 2.26 per 100 patient-years for naproxen (relative risk 0.43, 95% CI 0.27 to 0.67, NNT 77).

CLASS (Celecoxib Long-term Arthritis Safety Study). CLASS was designed as two trials with separate patient recruitment and randomization procedures: one compared celecoxib 400 mg twice a day with ibuprofen 800 mg three times a day, and the other compared celecoxib 400 mg twice a day with diclofenac 75 mg twice a day.⁵⁷ Because the FDA was concerned that selective COX-2 inhibitors could interfere with the benefits of COX-2 in ulcer healing and lead to a long term increase in GI complications without warning symptoms, the pre-specified primary outcome was “ulcer-related complications.”⁹⁹ Another pre-specified outcome was ulcer related complications plus symptomatic ulcers. The planned maximum duration of the trials were 15 and 12 months, respectively, or until at least 20 ulcer-related complications occurred in each trial, or 45 in both trials combined.¹⁰⁰ The protocols stated that celecoxib would be claimed to be different from traditional NSAIDs only if there were statistically significant differences between celecoxib and each of the comparators, as well as between celecoxib versus the comparator groups combined.

The CLASS trials were stopped early after the predefined threshold of ulcer complications occurred. However, the analysis and reporting of the results as presented in the main publication in JAMA were in part incomplete and differed in some ways from the protocols. The JAMA article reported truncated 6-month results even though the median duration of follow-up was 9 months (range 6 to 13 months), and combined the ibuprofen and diclofenac results without reporting the trial results separately.⁵⁷ Subsequently, additional details of the study have been made public on the FDA web site¹⁰⁰ and have been extensively analyzed. The findings of the FDA analysis suggest that the published results of CLASS are, in part, misleading because they appear to selectively report results at the point in time at which celecoxib was most effective.¹⁰¹⁻¹⁰³

There were 3,987 subjects randomized to celecoxib and 3,981 subjects randomized to non-selective NSAIDs in the CLASS trials. For the combined outcome of ulcer complications or symptomatic ulcers, the JAMA article reported that patients on celecoxib experienced fewer GI complications compared with patients in the combined NSAID groups (32/3987 versus 51/3981, annualized incidence rates 2.08% vs. 3.54%, $p=0.02$),⁵⁷ while the rate of complicated ulcers alone was not significantly different (13/3987 vs. 22/3981, annualized incidence rates 0.76% vs. 1.45%, $p=0.09$). However, by 12 months, according to FDA documents (see Table 14, FDA Medical Officer Review)¹⁰⁰ there was no longer a trend favoring celecoxib for the primary outcome of complicated ulcers. There were 17/3987 events in the celecoxib group (0.43%) versus 21/3981 (0.53%) in the NSAID groups combined.¹⁰⁰ This difference was not statistically significant (relative risk 1.10, 95% CI 0.47 to 2.58^{103, 104}, also see Figure 4, Scheiman review¹⁰⁵). For the individual comparisons between celecoxib and ibuprofen or diclofenac, which were not reported in the JAMA article, there was no difference in the rate of ulcer complications at either 6 months or at the end of follow-up.¹⁰³ For the outcome of ulcer complications or symptomatic ulcers, celecoxib was superior to ibuprofen, but not to diclofenac at either 6 months or at the end of follow-up.¹⁰³

Authors of CLASS have not completely explained the reasons for selective reporting of results, though they contend that combining the two trials and reporting ulcer complications plus symptomatic ulcers as a primary outcome were permitted by the protocols.^{106, 107} However, reporting only combined results obscured differences between the results for the two comparator drugs.¹⁰² The main argument for reporting truncated data is that results after 6 months were not interpretable because of high and differential rates of drop-outs due to symptomatic ulcers, which could have biased results against celecoxib because of depletion of high-risk patients in the non-

selective NSAID arms.^{106, 107} On closer inspection, however, this rationale appears flawed, as neither symptomatic ulcers nor gastrointestinal symptoms predicted ulcer complications.¹⁰² Furthermore, simply truncating data is not considered an acceptable method for resolving issues related to high drop-out rates.

Twenty per cent of the patients in the CLASS trial took aspirin in addition to their study drug. When patients taking aspirin were excluded from the analysis, there were fewer confirmed serious ulcer complications in the celecoxib group than in the ibuprofen group ($p=0.03$).^{100, 103} However, serious ulcer complications for celecoxib and diclofenac were equivalent even when patients taking aspirin were excluded from the analysis.

In summary, the CLASS trials did not demonstrate a statistically significant advantage over either diclofenac or ibuprofen for the primary endpoint of complicated ulcers for all patients enrolled. Celecoxib appeared superior to ibuprofen, but not diclofenac, in a subgroup of subjects not taking aspirin. In its decision regarding labeling for celecoxib, the FDA agreed with its Advisory Committee recommendations that CLASS did not demonstrate a safety advantage in upper gastrointestinal safety for celecoxib compared with either ibuprofen or diclofenac.¹⁰⁸

Comparison between VIGOR and CLASS. There are several possible reasons why rofecoxib (VIGOR), but not celecoxib (CLASS), significantly reduced ulcer complications. First, patient populations and study designs differed (Appendix G.) VIGOR included patients aged 50 or older with rheumatoid arthritis, while CLASS had a broader age range of patients with either osteoarthritis or rheumatoid arthritis. In addition, VIGOR prohibited the use of aspirin while CLASS did not. The rate of ulcers in the patients taking a control drug was almost three times as high in VIGOR as in CLASS, although rates of ulcer complications were similar. In addition, VIGOR compared rofecoxib to naproxen and CLASS compared celecoxib to diclofenac and ibuprofen. This could have affected the results if the non-selective comparator NSAIDs are associated with differential risk of ulcers. Finally, it is possible that rofecoxib, which has greater COX-2 selectivity, is truly more gastroprotective than celecoxib.

CV safety

CV risk in VIGOR. Findings from the VIGOR trial raised concerns that the putative GI safety benefits of COX-2 selective NSAIDs relative to non-selective NSAIDs may have come at the expense of increased cardiovascular events. The main publication of VIGOR¹⁸ reported that “the incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.” This corresponds to one additional heart attack for every 333 patients treated with rofecoxib instead of with naproxen. A re-analysis of VIGOR with three additional myocardial infarctions not included in the results originally submitted for journal publication estimated a relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen among all patients, and 3.00 (95% CI 0.91 to 12.78) among patients in whom aspirin was not indicated.¹⁰⁹ For patients who had indications for aspirin, 8 MIs occurred during 105 person-years of exposure to rofecoxib, compared with no MIs during 102 person-years of exposure to naproxen. Blinded adjudication of the VIGOR trial data classified 45/4047 (one in every 90) rofecoxib patients and 19/4029 (one in 212) naproxen patients as having serious thrombotic events (heart attack, stroke, unstable angina, transient ischemic attack, resuscitated cardiac arrest, and sudden death).¹¹⁰ This corresponds to

one additional serious thrombotic event for every 156 patients taking rofecoxib.

CV risk in CLASS. The original publication of the CLASS trials, using 6-month data, reported that celecoxib had no effect on the rate of myocardial infarction or for any cardiovascular event (stroke, myocardial infarction, or angina) compared with diclofenac and ibuprofen.⁵⁷ The number of myocardial infarctions was 10/3987 (0.3%) with celecoxib versus 11/3981 (0.3%) with the non-selective NSAIDs). The full CLASS data on thrombotic events were analyzed in more detail by White and colleagues,¹¹¹ who also found no differences in the rates of any significant cardiovascular event for the overall sample or for the subgroup who did not use aspirin. For the overall sample, myocardial infarctions occurred in 19/3987 (0.5%) of patients on celecoxib and 13 (0.3%) on diclofenac or ibuprofen. In fact, as discussed above, more detail about the design of the CLASS trials is necessary to judge the validity and generalizability of these results. In particular, reporting of longer-term data is important because 6 months of exposure to celecoxib may not be enough time to assess cardiovascular risk. At 8 months in the VIGOR trial there was no significant difference between rofecoxib and naproxen in the cumulative incidence of events. From 8 to 12 months, the incidence of events in the rofecoxib group rose sharply (Figure 1 of Mukherjee¹¹²), while that of naproxen did not. Based on the pattern observed in VIGOR, if celecoxib is associated with an increased risk of cardiovascular events, it may not be seen until 10 or 12 months of followup. In the VIGOR trial, 2,140 subjects, about one-fourth of the original sample, were available for 10 months of followup, and 1,045 were available for 12 months. In the CLASS trials, 2,770 subjects, about one-third of the original sample, had at least 9 months of follow-up, and 1,126 had at least 12 months of follow-up, suggesting that an analysis should have been able to detect an increased risk of cardiovascular events similar to that observed in VIGOR, if it was present (see Table 4, FDA Medical Officer Review¹⁰⁰).

White and colleagues argue that their meta-analysis shows that celecoxib is safer than rofecoxib.¹¹¹ To support their argument, they note that the annualized rate of all cardiovascular thromboembolic events in the naproxen group in the VIGOR trial and the non-aspirin celecoxib users in the CLASS trial were similar. However, this comparison of rates across the VIGOR and CLASS studies is imprecise. After 8 months in the VIGOR trial, about 0.4% of naproxen patients had experienced an event; after 8 months in CLASS, about 0.8% of non-aspirin users had. It is not clear whether or not this is a clinically or statistically significant difference. By contrast, Mukherjee and colleagues suggested that the selective NSAIDs as a class might be associated with an increased risk of myocardial infarction because the 0.8% rate of myocardial infarction on celecoxib in the CLASS trials and the 0.74% rate on rofecoxib in VIGOR are both higher than the 0.52% rate observed in a meta-analysis¹¹³ of patients receiving placebo in studies of aspirin prophylaxis.¹¹² In our opinion, all of these conclusions are unsubstantiated because they involve cross-trial and historical comparisons.

Overall rate of serious adverse events in CLASS and VIGOR. One analysis from Canada used FDA materials to analyze the rates of serious adverse events, defined as death, hospitalization, or “any life-threatening event, or event leading to severe disability” in the CLASS and VIGOR trials.¹¹⁴ This measure combines the rates of serious upper GI complications (in which coxibs are expected to have an advantage over NSAIDs) with other serious adverse events. The numbers of all serious adverse events were drawn directly from FDA materials, pages 7 and 8 (rofecoxib¹¹⁵) and 57 (celecoxib¹⁰⁰).

In the Canadian re-analysis, shown in Table 4, the rates are calculated using the number of patients as the denominator. These simple risks are compared with the number of serious upper

GI events, which constitute only about 10% of all serious adverse events (the two columns to the right in the table). Using all serious adverse events as the criterion for “harm,” the number-needed-to-harm one person was 82 for celecoxib vs. diclofenac, 129 for celecoxib vs. ibuprofen, 100 for celecoxib vs. diclofenac and ibuprofen, and 65 for rofecoxib vs. naproxen. The Canadian authors also pooled the results for celecoxib and rofecoxib, assigning more weight to VIGOR, which had a longer duration than CLASS. In the pooled analysis, the number needed to harm was 78 for the selective COX-2 inhibitors versus non-selective NSAIDs and was statistically significant.

Table 4. Re-analysis of the CLASS and VIGOR Trials

Trial	ALL SERIOUS ADVERSE EVENTS		SERIOUS UPPER GI EVENTS	
	Treatment	Control	Treatment	Control
CLASS ⁵⁷	270/3987 (6.8%)	230/3981(5.8%)	20/3987 (0.5%)	24/3981 (0.6%)
VIGOR ¹⁸	378/4047 (9.3%)*	315/4029 (7.8%)	16/4047 (0.4%)*	37/4029 (0.9%)

*statistically significant vs. control group.

For the VIGOR trial, the FDA calculated rates of serious adverse events in exactly the same manner as the Canadian investigators.¹¹⁵ The FDA analysis shows that the rates of each serious adverse event (except GI adverse events) were higher for rofecoxib than for naproxen. For the CLASS trials, the FDA used normalized patient-years as the denominator instead of a simple proportion to calculate rates of serious adverse events.¹⁰⁰ This approach was used because the two trials that make up CLASS had different durations. In the FDA analysis, the rates of all serious adverse events combined were 11.6 per 100 patient-years for celecoxib; 10.3 per 100 patient-years for diclofenac, and 10.6 per 100 patient-years for ibuprofen, a difference the FDA interpreted as being statistically insignificant.

In summary, the FDA data clearly show that these two coxibs, in doses higher than those commonly used in practice, do not reduce the overall rate of serious adverse events, and may have increased them. It should be noted, however, that not all serious adverse events are equal in importance to patients and physicians. A reduction in the rate of one kind of adverse event might be considered more important than an increase in another one.

Rofecoxib and celecoxib: Further analyses of CV toxicity and GI safety

The GI and CV risk profiles of celecoxib and rofecoxib relative to one another and to NSAIDs, placebo, or no treatment have also been assessed in numerous meta-analyses of randomized trials and observational studies. We were unable obtain final results of the two most recent relevant meta-analyses in time to include them in this report. Preliminary results of one systematic review of cardiovascular risks associated with selective and non-selective NSAIDs in over 130 randomized clinical trials were recently presented to a Canadian Consensus Conference. We were unable to obtain the full results of this review, though a summary of the results has been published.¹¹⁶ The other systematic review evaluated the GI safety associated with selective and non-selective NSAIDs.¹¹⁷ Analyses of GI safety with celecoxib and rofecoxib in this study were based on results from CLASS,⁵⁷ VIGOR,¹⁸ the unpublished SUCCESS-1 trial of celecoxib,⁶⁷ and two previously published meta-analyses.^{118, 119}

Systematic reviews and meta-analyses of GI safety.

Rofecoxib. VIGOR remains the only individual trial large enough to adequately assess rates

of upper GI complications with rofecoxib and non-selective NSAIDs in patients with arthritis. However, the manufacturer of rofecoxib also conducted a prospective meta-analysis of GI safety from eight smaller phase 2b/3 osteoarthritis trials (N=5425).¹¹⁹ It found that the 12-month combined incidence of perforations, symptomatic ulcers, and upper GI bleeding was significantly lower with rofecoxib compared with non-selective NSAIDs (1.3% vs. 1.8%, P=0.046; rate per 100 patient-years 1.33 vs. 2.60, RR 0.51, 95% CI 0.26 to 1.00). The rate of ulcer complications alone, however, was not reported. A Food and Drug administration review has been critical of several aspects of this meta-analysis.¹²⁰ It notes that it is not clear how assiduously investigators of the trials adhered to the pre-specified protocols, and that most cases were unblinded before the adjudication process occurred. In addition, the FDA review suggests that simple pooling and comparisons of the rofecoxib and the non-selective NSAIDs outcomes may be misleading because study duration varied, different patient withdrawal criteria were applied, different diagnostic surveillance methods (including endoscopic surveillance in two trials) were employed, doses of rofecoxib varied, and different comparator NSAIDs were used. Rates of complicated ulcers at 12 weeks, for example, were substantially higher in patients on ibuprofen (1.12%) compared with diclofenac (0.19%). Further, combining symptomatic ulcers and ulcer complications may be misleading because the morbidity associated with ulcer complications is substantially higher than the morbidity associated with symptomatic ulcers. Data reported on the FDA web site (page 78) indicate that only six complicated ulcers in 3,357 patients on rofecoxib and five in 1,564 patients on non-selective NSAIDs (cumulative incidence at 12 months 0.45% vs. 0.55%) occurred; the difference was not statistically significant (relative risk using Cox proportional hazards model 0.51, 95% CI 0.16 to 1.69).¹²⁰

The only randomized controlled trial evidence demonstrating a lower risk of complicated ulcers with rofecoxib compared with non-selective NSAIDs therefore comes from VIGOR. Differences between the results of VIGOR and the meta-analysis of the phase 2b/3 trials could be due in part to the low number of complicated ulcers in the meta-analysis (in other words, insufficient power to detect a statistically significant difference), the longer duration of VIGOR than most of the trials in the meta-analysis (only 27% of patients were evaluated for one year), or the higher dose of rofecoxib used in VIGOR (only 16% of the subjects randomized to rofecoxib in the meta-analysis received the 50 mg dose).

Celecoxib. One manufacturer-funded meta-analysis examined the endpoint of “UGI ulcer complications” in 14 RCTs of celecoxib (not including CLASS) versus placebo or non-selective NSAIDs (usually naproxen).¹²¹ The trials ranged in duration from 2 to 24 weeks, with most lasting 6 or 12 weeks. The strength of this meta-analysis was that the endpoint—upper GI bleeding with endoscopic findings of an ulcer or large erosion, perforation, or gastric outlet obstruction—was similar to those used in the VIGOR and CLASS trials. A Safety Committee adjudicated potential ulcer complications in a blinded manner. These endpoints were ascertained through a monitoring program that appears to have been superimposed on all of the trials; it is not clear how assiduously investigators complied with this program. As mentioned above, not all of these trials have been published, and their quality was not assessed as part of the meta-analysis. In addition, like the meta-analysis of rofecoxib trials described above, results of the trials were simply pooled despite differences in dose of rofecoxib, duration of therapy, or which comparator NSAID was used. In the 14 trials, there were 2/6,376 UGI ulcer complications in the celecoxib group (3 per 10,000) and 9/2,768 in the NSAIDs group (33 per 10,000) and none in the placebo group (0/1,864). This corresponded to annual rates of two per 1,000 per year for celecoxib and about 17 per 1,000 per year for NSAIDs (p=0.002).

There are several possible reasons why the results of the meta-analysis were different from those of CLASS. First, the incidence of serious ulcer complications in CLASS was much higher than in the trials included in the meta-analysis. In the CLASS trials, the annualized rate of serious ulcer complications was 7.6 per 1,000 per year for celecoxib and 14.5 per 1,000 per year for the two NSAIDs combined.⁵⁷ The nearly four-fold higher rate of ulcer complications in the CLASS trial compared with other celecoxib trials could be due in part to enrollment of a higher-risk population, the use of concomitant medications, the dose of celecoxib evaluated, or other factors. In CLASS, for example, 21% of patients randomized to celecoxib were on aspirin and 30.6% on corticosteroids. By contrast, only 12.4% of patients in the meta-analysis were taking aspirin, and 13.5% on corticosteroids.¹²¹ In addition, antiulcer medications (except for occasional antacids) were prohibited in CLASS, but used in 16.5% of celecoxib patients in the meta-analysis. Another potential explanatory factor is that the high dose of celecoxib used in CLASS—400 mg twice daily—was evaluated in only about 10% of the patients in the meta-analysis. It is possible that using higher doses of celecoxib could attenuate GI safety benefits because of incomplete COX-2 selectivity. Finally, different comparator NSAIDs could be associated with different risks of GI complications. In the meta-analysis, six trials (N=6151) compared celecoxib to naproxen versus only three trials (N=2439) that compared celecoxib to diclofenac or ibuprofen (the drugs evaluated in CLASS). Pooling data from trials evaluating different comparator NSAIDs could obscure differential effects on GI safety if they are present.

Moore, McQuay and others conducted a separate meta-analysis of celecoxib trials for osteoarthritis or rheumatoid arthritis, with funding from Pfizer and the Oxford Pain Relief Trust.⁶⁶ The authors obtained a declaration from Pfizer that they had received information on all completed clinical trials of celecoxib and would be permitted to publish the results no matter what their findings showed. However, much of the data on which this meta-analysis was based remains inaccessible to the public. They reviewed over 180,000 pages of company documents, which included detailed information on study methods. All 31 included trials were rated 5 out of 5 on the Jadad quality scale, and 16 out of 16 on an eight-item validity scale. They found that celecoxib was associated with a lower risk of hemoglobin fall of 20 g/L or more (a marker for a significant GI bleed) (RR 0.72, 95% CI 0.56 to 0.92) and hematocrit fall of 5% or more (RR 0.78, 95% CI 0.69 to 0.89) compared with non-selective NSAIDs.⁶⁶ Although this review did not evaluate complicated ulcers as a separate outcome, celecoxib was also associated with a lower risk of clinical ulcers and bleeds than non-selective NSAIDs in 18 trials (RR 0.61, 95% CI 0.46 to 0.81). When the analysis was limited to trials evaluating doses of 200 or 400 mg daily of celecoxib (in other words, excluding the results of CLASS), the benefit was more pronounced (RR 0.35, 95% CI 0.22 to 0.56).

Other than CLASS, only one other randomized controlled trial (SUCCESS-1) was designed to assess ulcer complications. However, results of this trial have only been reported in abstract form.⁶⁷ In this large (N=13,274), 12-week trial of patients with osteoarthritis, celecoxib was associated with a lower incidence of ulcer complications than naproxen or diclofenac (0.1% versus 0.8%, OR 7.0, 95% CI 1.5 to 33.8). Because details of this trial have not been published (a report submitted to the FDA notes that a manuscript based on these trials has been rejected by three separate journals¹²²), the validity of these findings are uncertain.

Systematic reviews and meta-analyses of CV toxicity.

Rofecoxib. VIGOR and other randomized trials of rofecoxib have been extensively re-

examined to further explore its cardiovascular risk profile. Many questions have been raised in response to the disparate findings of these analyses and a myriad of possible explanatory factors have been proposed.

In October 2001, an article published in *Circulation*¹²³ by Konstam and colleagues reported a pooled analysis from 23 rofecoxib Phase IIb through V trials sponsored by Merck. The investigators examined results by patient group (rheumatoid arthritis, osteoarthritis, or Alzheimer's disease) and by control group (placebo, naproxen, or non-naproxen NSAID). The risk of cardiovascular events was 1.69 times higher for rofecoxib than for naproxen (95% CI 1.07 to 2.69), but was not elevated in trials comparing rofecoxib versus placebo (RR 0.84, 95% CI 0.51 to 1.38) or non-naproxen NSAIDs (RR 0.79, 95% CI 0.40 to 1.55). The authors hypothesized that rofecoxib might have been an "innocent bystander" in the VIGOR trial. In other words, rather than rofecoxib increasing the rate of cardiovascular events, naproxen might have reduced it.

A problem with the Konstam analysis¹²³ is that the non-naproxen and naproxen studies are not directly comparable. VIGOR, the only COX-2 trial to demonstrate a significant reduction in serious GI events, used rofecoxib 50mg, prohibited aspirin, and followed patients for 9 months. By contrast, the non-naproxen-controlled studies were shorter than 6 weeks in duration or used lower doses of rofecoxib. An exception was eight phase IIb/III trials in osteoarthritis patients (see below). The data presented in the meta-analysis are also inadequate to judge the quality of the included studies and how concomitant aspirin use (or other factors) might have affected rates of cardiovascular events, as adjustment using individual patient risk factors was not performed.

A subsequent meta-analysis by Reicen and colleagues provided a more detailed analysis of eight phase IIb/III trials of osteoarthritis patients previously included in the Konstam analysis.¹²⁴ The total number of subjects in the eight trials is given as 5,435, versus 5,505 in the Konstam analysis. The reason for the discrepancy in sample sizes is unclear, and there is no detailed accounting of the excluded subjects. The mean duration of treatment was 3½ months. Like the Konstam study, insufficient information was provided to judge the quality of the studies analyzed or the effects of concomitant aspirin. The incidence of thrombotic cardiovascular adverse events was lower in the rofecoxib treatment group (1.93/100 patient-years) compared with the non-naproxen NSAID (ibuprofen, diclofenac, or nabumetone) groups (2.27/100 patient-years).

The conclusion of the Reicen analysis—that there were no significant differences between rofecoxib and placebo or non-naproxen NSAIDs—may be valid for this set of studies. However, the results do not address the more specific question of whether rofecoxib is safe at the dosage proven to reduce serious GI events. The analysis combined data from all rofecoxib doses (12.5, 25, and 50mg/day); only 545 of the patients received the 50mg/day dose. The issue of dosage is important because only the 50mg dose has been shown to prevent serious GI adverse events.¹⁸ It is possible that lower doses do not increase cardiovascular events compared with non-naproxen NSAIDs, but the benefit of lower, conventional doses for reducing GI adverse events is also uncertain.

Using a different methodology from the studies by Konstam and Reicen, a meta-analysis funded by the Swiss National Science Foundation came to different conclusions.¹²⁵ Juni and colleagues included 18 randomized controlled trials of rofecoxib in patients with chronic musculoskeletal disorders (N=25,273), using published data on myocardial infarction as well as unpublished data available from the FDA. They found that the risk of myocardial infarction was higher in patients in the rofecoxib arms of trials compared with patients in the combined

comparator arms (naproxen, non-naproxen NSAIDs, or placebo) (RR 2.24, 95% CI 1.24 to 4.02). The risk did not vary according to dose of rofecoxib or duration of therapy (shorter versus longer than 6 months). Trials with an external endpoint committee had a substantially higher risk for myocardial infarction (RR 3.88, 95% CI 1.88 to 8.02) than those without an external endpoint committee (RR 0.79, 95% CI 0.29 to 2.13). VIGOR contributed 8,076 of the 21, 432 included in the meta-analysis. However, the increased risk of myocardial infarction in trials with an external endpoint committee persisted (RR 2.5, 95% CI 1.1 to 6.0) even when the results of VIGOR were excluded.¹²⁶

Unlike the previous meta-analyses by Reicen and Konstam, the Juni meta-analysis analyzed study-level data and assessed the outcome of myocardial infarction (rather than composite cardiovascular endpoints, which could have diluted the effects on myocardial infarction rates). A major point of contention, however, centers on whether the Juni meta-analysis inappropriately combined results from different control interventions. Although Reicen and others have criticized this method of analysis because different control interventions may be associated with different risks for myocardial infarction,¹²⁷ Juni and colleagues' methods appear defensible based on their multivariate meta-regression analyses of potential sources of heterogeneity. They found that the only significant source of variation between study results was related to the use of an independent, external endpoint committee, and not to the type of control intervention. For studies with an external endpoint committee, the relative risk for myocardial infarction for rofecoxib compared with placebo, non-naproxen NSAIDs, or naproxen was similar (2.31, 2.98, and 3.72, respectively, with overlapping confidence intervals).¹²⁶ The Reicen and Konstam meta-analyses did not assess the effects of this potentially important source of bias.

An increased risk of cardiac events (myocardial infarction, sudden death from cardiac causes, or unstable angina pectoris) was also observed in a long-term, placebo-controlled trial of a different population—that of patients receiving rofecoxib for prevention of colon polyps. The Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial found that the risk of cardiac events was 2.80 (95% CI 1.44 to 5.45) with rofecoxib 25 mg day compared with placebo, though the rate of events only diverged after 18 months. The rate of cerebrovascular events and peripheral vascular events were not significantly higher on rofecoxib (RR 2.32, 95% CI 0.89 to 6.74 and 0.46, 95% CI 0.08 to 2.03, respectively).

Celecoxib. Three meta-analyses, all funded by the manufacturer of celecoxib, have analyzed the cardiovascular risks associated with celecoxib in primarily unpublished trials. The first, by White and others, included 13 new drug application studies and two large post-marketing trials (CLASS and SUCCESS) of 18,942 patients randomized to celecoxib with osteoarthritis or rheumatoid arthritis.¹²⁸ Only two of the 15 trials were longer than 12 weeks in duration. The meta-analysis did not provide enough information about the design of the included studies to judge their quality. It found no difference in risk of cardiovascular events (cardiovascular, hemorrhagic and unknown deaths; nonfatal MI, or nonfatal stroke), fatal myocardial infarction, or nonfatal myocardial infarction between patients randomized to celecoxib versus those randomized to placebo, all NSAIDs, or naproxen (Table 5). There were also no differences in the subgroup of patients who were aspirin non-users. The authors did not perform an analysis of risk associated with different doses of celecoxib.

Table 5. CV events in trials of celecoxib: meta-analysis of 15 trials in patients with arthritis¹²⁸

Comparison	Relative risk for cardiovascular, hemorrhagic and unknown deaths; nonfatal MI; or nonfatal stroke (95% CI)

All patients	
Celecoxib versus placebo	0.85 (0.23 to 3.15)
Celecoxib versus all NSAIDs	1.06 (0.70 to 1.61)
Celecoxib versus naproxen	0.85 (0.29 to 2.46)
Aspirin nonusers	
Celecoxib versus placebo	0.60 (0.11 to 3.29)
Celecoxib versus all NSAIDs	0.86 (0.48 to 1.56)
Celecoxib versus naproxen	0.82 (0.18 to 3.70)

The second, more comprehensive meta-analysis was presented to the FDA's Arthritis Advisory Committee in February 2005.¹²² It included 41 trials of celecoxib (N=24,933) for chronic conditions; 33 of the trials were in patients with osteoarthritis or rheumatoid arthritis. Only four of the 41 trials were longer than 12 weeks in duration. The investigators used full follow-up data from the CLASS trials (2,320 patient-years for 3,987 patients). In addition to the composite outcome of any cardiovascular thromboembolic event, the analysis also reported separate analyses for myocardial infarction, stroke, and peripheral vascular events. Over 80% of the cardiovascular events occurred in three large trials: CLASS (N=7,968), SUCCESS (N=13,194), and CAESAR (N=916) (the latter two studies remain unpublished). The methods and limitations of this study were similar to the White meta-analysis. There were no significant differences between celecoxib and comparators for myocardial infarction, though event rates were low: only nine myocardial infarctions occurred among 7,462 celecoxib-exposed patients (0.12%). There were also no significant differences for any other cardiovascular thromboembolic event.

Table 6. CV events in trials of celecoxib: meta-analysis of 41 trials¹²²

Comparison	Relative risk for myocardial infarction (95% CI)
All patients	
Celecoxib ≥200 mg/day versus placebo	1.58 (0.92-2.72)
Celecoxib ≥200 mg/day versus non-selective NSAIDs	1.65 (0.38-7.21)
Aspirin nonusers	
Celecoxib ≥200 mg/day versus placebo	1.40 (0.61-3.21)
Celecoxib ≥200 mg/day versus non-selective NSAIDs	1.64 (0.17-15.33)

Another meta-analysis of manufacturer-held clinical trials reports by Moore and colleagues found that celecoxib was not associated with an increased risk for myocardial infarction compared with non-selective NSAIDs, any active comparator (including rofecoxib or paracetamol), any comparator (including placebo), or any non-coxib comparator using a fixed-effect model (Table 7).⁶⁶ They found too few events in trials comparing celecoxib to placebo (10 events), paracetamol (0 events), or rofecoxib (1 event) to analyze differences in myocardial infarction risk. The overall proportion of patients randomized to celecoxib with myocardial infarction was less than 0.3%. In the included trials, myocardial infarctions were as reported by investigators, and were not subject to adjudication. Although the duration of included trials varied, the mean duration of exposure was about 7 months. The authors of the meta-analysis were unable to perform an analysis according to duration of exposure, because the trial reports generally did not provide information to allow calculation of median duration of use.

Table 7. MI's in trials of celecoxib: meta-analysis of 31 trials in patients with arthritis⁶⁶

Comparison	Relative risk for myocardial infarction
Celecoxib 200 or 400 mg/day versus NSAID	1.9 (0.87 to 4.1)
Celecoxib any dose versus NSAID	1.6 (0.93 to 2.6)
Celecoxib any dose versus any active comparator	1.4 (0.87 to 2.3)
Celecoxib any dose versus any comparator	1.4 (0.88 to 2.2)
Celecoxib any dose versus non-coxib comparator	1.4 (0.88 to 2.2)

In summary, celecoxib does not appear to be associated with an increased risk of myocardial infarctions or thromboembolic cardiovascular events in primarily short-term studies (seven months or less) of arthritis patients. However, the importance of analyzing longer-term data and assessing dose effects are underscored by the results of a long-term trial in a different population—that of patients receiving celecoxib for colorectal polyp prevention.¹²⁹ This trial, which randomized patients to celecoxib versus placebo, was terminated after 33 months because of a higher rate of cardiovascular events in the celecoxib arms. According to the Figure 2 in the main publication of this trial,¹²⁹ the rates of events appeared to rise more rapidly in the celecoxib arms compared with the placebo arm only after nine months. The risk also appeared to be dose-dependent: compared with placebo, the risk was higher in patients randomized to celecoxib 400 mg bid (RR 3.4, 95% CI 1.4 to 8.3) than in patients randomized to celecoxib 200 mg bid (RR 2.5, 95% CI 1.0 to 6.3). On the other hand, preliminary data from two other prevention trials (ADAPT, an Alzheimer's prevention trial,¹³⁰ and PreSAP, another polyp prevention trial¹³¹), neither of which has been published, found no increased cardiovascular risk with celecoxib 400 mg daily compared with placebo. It is not clear why the results of these trials differed from the APC trial, though full publication of results may prove to be more informative.

Observational studies of GI and CV safety

Overview. Numerous long-term observational studies have evaluated the GI and CV risks associated with selective and non-selective NSAIDs. The studies primarily relied on claims data or other administrative databases or on electronic medical record data collected in practice networks to identify cases, and prescription claims to determine exposure. A strength of these studies is that they evaluated much larger populations than could be enrolled into clinical trials.¹³² In addition, they reflect how coxibs and other NSAIDs are actually used in practice better than many clinical trials, which are usually short term, specify rigid dosing regimens, limit the use of other drugs, and implement co-interventions to monitor and enhance compliance. Population- and practice-based studies may better represent patients who would be excluded from randomized trials because of comorbidities, age, and other characteristics.

On the other hand, the most important weakness of observational studies is that patients are allocated treatment in a non-randomized manner. This can lead to biased estimates of effects even when appropriate statistical adjustment on a variety of confounding variables is performed.¹³³ In addition, the data sources cannot reliably assess over-the-counter aspirin, NSAIDs, or acid-suppressing medication use,¹³² and information on prescription fills may not always accurately correspond to the actual degree of exposure to the drugs.

Rofecoxib Four observational studies reported rates of serious GI events for rofecoxib relative to celecoxib, NSAIDs, and non-use.¹³⁴⁻¹³⁷ Appendix H provides a detailed description of study characteristics and outcomes and the main findings are summarized below (Table 8). In direct comparisons, rofecoxib was associated with a risk of upper GI complications similar to meloxicam,¹³⁶ but had a greater risk of upper GI hemorrhage than celecoxib, non-selective

NSAIDs, and diclofenac plus misoprostol.¹³⁵ In a nested case-control studies that assessed GI event rates, the risk of upper GI bleeding was modestly higher for rofecoxib than celecoxib, NSAIDs, or non-use (RR in the range of 1 to 2.)^{134, 137} Another case-control study that found a higher relative risk should be interpreted with caution because exposure information was ascertained using unblinded patient interviewing, which is more susceptible to recall bias than blinded coding of prescription/general practice databases.¹³⁷

Subgroup analyses of patients with mitigating risk factors such as exposure duration, dosage, and study duration were generally not reported. In fact, COX-2 dosages were only reported in one study and proportions of patients were 19% for celecoxib (> 200 mg) and 8% for rofecoxib (> 25 mg).¹³⁵

Table 8. Serious GI events in observational studies

Author, Year Study design Sample size	Mean age (yrs)	Duration (days)	Outcome	Main findings
Hippisley-Cox 2005 ¹³⁴ Case-control Cases: 9407	NR; ≥ 25	Unclear	Complicated GI event	↑ <i>risk relative to non-use</i> : No for celecoxib Yes for rofecoxib; overall selective and non-selective NSAIDs; ibuprofen; diclofenac; naproxen
Mamdani 2002 ¹³⁵ Cohort n=143,969	75.7	141	Upper GI hemorrhage	↑ risk for rofecoxib relative to celecoxib, non-selective NSAIDs and diclofenac+misoprostol
Layton 2003 ¹³⁶ Cohort n=34,355	60.4-62.5	270	Upper GI complications (perforations/bleeding)	Similar risk for rofecoxib and meloxicam
Laporte 2004 ¹³⁷ Case-control Cases=2,813	NR; ≥ 18	NR	Upper GI bleeding	↑ <i>risk vs. non-use</i> for rofecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, nimesulide, piroxicam

Ten observational studies evaluated risk of cardiovascular events associated with rofecoxib (Table 9.).¹³⁸⁻¹⁴⁷ Interpretation of the studies is complicated by the use of different study designs, adjustment for different confounders, and evaluation of different populations and outcomes. Six of these studies appeared to rely exclusively on administrative and pharmaceutical databases to determine outcomes, exposures, and comorbidities.^{138, 142, 144-147} The other four studies supplemented administrative or claims data with chart review;¹⁴⁰ clinical or practice-based databases,^{141, 143} or telephone interviews.¹³⁹ Several studies indicate that using claims data is quite accurate (positive predictive value >90%) for identifying myocardial infarction.^{148, 149} A weakness of relying exclusively on administrative databases, however, is that they frequently have incomplete information about potentially important confounders such as income level, obesity, smoking status, and level of education.¹⁴⁹ All three of the observational studies that collected information about body mass index, for example, supplemented administrative databases with other sources.¹³⁹⁻¹⁴¹ Unmeasured confounders could result in less accurate estimates of cardiovascular risk, though one analysis suggests that the effects would be modest.¹⁵⁰ On the other hand, studies can also ‘overcontrol’ if they adjust for cardiovascular risk factors identified after the initiation of treatment, if these are intermediate effects of the drugs themselves that predispose to subsequent cardiovascular events.¹⁵¹

Rofecoxib was associated with an increased risk of CV events relative to non-selective NSAIDs in two of four studies^{139, 147} and an increased risk relative to celecoxib in three of three studies.^{139, 140, 152} In studies that compared rofecoxib, celecoxib, or NSAID use to non-use, none of the drugs were consistently associated with increased risk of CV events.^{138, 141, 142, 144, 146} CV event risk estimates from two observational studies of rofecoxib relative to naproxen (Solomon 2004¹⁴⁰: OR 1.17, 95% CI 0.90, 1.52; Kimmel 2005¹³⁹: OR 3.30, 95% CI 1.37, 8.40) were lower than the estimated relative risk for myocardial infarction of 5.00 (95% CI 1.68 to 20.13) for rofecoxib compared with naproxen in VIGOR.¹⁰⁹ It is likely that the inconsistencies in effect magnitudes were due in large part to population differences and study methodology. Risk estimates from the Solomon 2004 study¹⁴⁰ may only be generalizable to a population that is of a more advanced age than that of VIGOR (81.6 vs. 58 years) and of a possibly lower income level, as it focused on low-income Medicare beneficiaries. Participants in the Kimmel 2005 study¹³⁹ were similar in mean age to those in VIGOR (53.1 vs. 58 years), but different methods of data ascertainment may have affected risk estimates. This study, which found the highest risk of MI associated with rofecoxib compared with celecoxib (OR 2.72), differed from the others in that it collected information about exposures and covariates using structured telephone interviews rather than by using administrative or large practice databases.¹³⁹ The use of structured telephone interviews could have enhanced the ability of the investigators to measure relevant confounders and drug exposures. On the other hand, participation bias (only 50% of those approached participated) and recall bias could also have skewed the results, though it is not clear that such biases would favor either rofecoxib or celecoxib.

Results of a study that found similar risk of CV events with rofecoxib and meloxicam may also be less reliable.¹⁴⁷ Unlike the other observational studies, which adjusted for multiple demographic factors and comorbidities, results for this study were only adjusted for recent prescription of other oral NSAIDs, age, and gender.

Another factor that varied between studies was how exposure status was defined. In one of the studies that reported no association between rofecoxib use and cardiovascular thrombotic events, use of selective COX-2 inhibitors was defined as prescriptions within 6 months of the index date.¹⁴⁵ By contrast, other studies defined current use as occurring on or near the index date, which strengthens confidence in inferences about the link between rofecoxib and the observed MIs.

Table 9. Cardiovascular events in observational studies

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Levesque 2005 ¹³⁸ Cohort n=59724	NR; ≥ 66	22.50%	844.8	Acute MI, fatal or nonfatal ↑ risk relative to NSAID non-use: Yes for rofecoxib, regardless of dose No for celecoxib, naproxen or meloxicam
Kimmel 2005 ¹³⁹ Case-control Cases: 1718	NR; aged 40 to 75	33.60%	NR	Nonfatal MI ↑ risk for rofecoxib when directly compared with celecoxib or naproxen ↑ risk relative to (A) ibuprofen or diclofenac or (B) naproxen Yes for rofecoxib and no for celecoxib; both regardless of aspirin use

Author, Year Data source Sample size	Mean age	Rate of aspirin use (% pts)	Exposure (days)	Main findings
Solomon 2004 ¹⁴⁰ Case-control Cases=10,895	NR; > 80	NR	1-30 days 31-90 days > 90 days	Acute MI ↑ risk for rofecoxib when directly compared with celecoxib ↑ risk relative to (A) naproxen, (B) ibuprofen or (C) other NSAIDs: No for either rofecoxib or celecoxib
Hippisley-Cox 2005 ¹⁴¹ Case-control Cases: 9218	NR; aged 25-100	NR	NR	First ever MI ↑ risk relative to nonuse: Yes for rofecoxib, other selective NSAIDs, ibuprofen, diclofenac, naproxen and other non-selective NSAIDs No for celecoxib
Mamdani 2003 ¹⁴² Cohort n=166,964	NR; ≥ 66	14.70%	165.6	Incidence of hospitalization for acute MI Similar risk for rofecoxib, celecoxib, naproxen, and non-naproxen non-selective NSAIDs relative to nonusers
Graham 2005 ¹⁵² Case-control Cases=8,143	NR: 18-84	Telephone interview subgroup (n=817): 23%	Mean=113 days before event	Acute MI requiring admission or sudden cardiac death ↑ risk for overall and high-dose (> 25 mg) rofecoxib users, ibuprofen, naproxen, and other NSAIDs relative to celecoxib
Johnsen 2005 ¹⁴⁴ Case-control Cases=10,280	69.6	6.9% high dose	NR	Acute MI ↑ risk relative to nonusers: Yes for current and new users of rofecoxib, new users of celecoxib, and current and new users of other non-aspirin NSAIDs No for current users of celecoxib or any users of naproxen
Shaya 2005 ¹⁴⁵ Cohort n=6,250 50% black	NR; 70% were aged 50 years or younger	NR	≥ 60 prior to event	Cardiovascular thrombotic events No ↑ risk for rofecoxib or celecoxib relative to other NSAIDs (excluding naproxen)
Ray 2002 ¹⁵³ Cohort n=378,776	61.5	NR	NR	Serious CHD (hospital admission for AMI or death from CHD) ↑ risk relative to NSAID non-use: No for rofecoxib (regardless of dose), celecoxib, ibuprofen and naproxen
Layton 2003 ¹⁴⁷ Cohort n=34,355	NR	NR	270	Thromboembolic events: (A) cardiovascular; (B) cerebrovascular; (C) peripheral venous thrombotic ↑ risk for rofecoxib relative to meloxicam for cardiovascular and cerebrovascular events; similar risks for peripheral venous thrombotic events

Celecoxib. As summarized above, celecoxib was consistently associated with lower risks of serious GI¹³⁵ and CV events^{139, 140, 152} than rofecoxib in several observational studies. Observational studies also demonstrated that, compared with NSAIDs, celecoxib was

consistently GI protective^{135, 154} or neutral¹³⁴ and was never associated with higher risks of CV events.^{139, 140, 145, 152}

With regard to GI safety, celecoxib was associated with significantly lower risks of GI hemorrhage when directly compared with non-selective NSAIDs (Risk Ratio of NSAIDs to celecoxib 4.4, 95% CI 2.3, 8.5)¹³⁵ and of perforations/bleeding when directly compared with meloxicam (RR 0.56; 95% CI 0.32, 0.96).¹⁵⁴ Risk of complicated GI events was significantly lower for NSAID nonuse relative to numerous NSAIDs (i.e., selective NSAIDs, ibuprofen, diclofenac, naproxen, non-selective) but was similar relative to celecoxib.¹³⁴

With regard to CV safety, celecoxib was associated with similar risks (estimate range 0.77 to 1.19) of serious CV events than ibuprofen, diclofenac, naproxen, and “other NSAIDs”^{139, 140, 145} and, in one study, was associated with significantly lower risks of acute MI requiring admission or sudden cardiac death than ibuprofen, naproxen, or other NSAIDs.¹⁵² Celecoxib was also consistently associated with similar risks of serious CV events relative to non-use,^{138, 141, 142, 144} with one exception.¹⁴⁴ In a case-control study based on data from Denmark National Health Service registries (mean age=69.6%), “new” use of celecoxib (filled *first* prescription within 30 days) taking celecoxib was associated with a higher risk of acute MI (RR 2.13; 95% CI 1.45, 3.13) than nonusers; whereas, “current” use of celecoxib (filled prescription within 30 days) was not.¹⁴⁴

Additional analysis of observational studies. An important limitation of the observational studies is that they did not simultaneously assess the risk for serious cardiac and GI events. We re-analyzed data from three studies that reported rates of acute myocardial infarction,¹⁴² hospital admissions for congestive heart failure,¹⁵⁵ and upper gastrointestinal bleeding¹³⁵ in a large cohort of elderly patients in Ontario, Canada, to estimate the net effects of selective and non-selective NSAIDs on serious cardiovascular and GI events in this population. Although the three studies evaluated the cohort at slightly different points in time, study methods and populations characteristics appeared essentially identical.

We calculated the effects of selective and non-selective NSAIDs on numbers of acute myocardial infarction, upper GI bleed, and hospitalization for heart failure using baseline rates of events in patients not exposed to NSAIDs and estimates of risk as reported in the studies (Table 10). We then estimated the net effects on all three serious adverse events using Monte Carlo simulation (see Methods section for additional details).

Table 10. Baseline rates of MI, upper GI bleed, and congestive heart failure (CHF) and risk associated with selective and non-selective NSAIDs in an Ontario cohort of elderly persons

Adverse event	Study, year	Baseline rates (per 1000 person-years)	Risk with celecoxib	Risk with rofecoxib	Risk with non-selective NSAIDs	Risk with naproxen
Myocardial infarction	Mamdani, 2003 ¹⁴²	8.2	0.9 (0.7 to 1.2)	1.0 (0.8 to 1.4)	1.5 (1.2 to 1.8)	1.0 (0.6 to 1.7)
Upper GI bleed	Mamdani, 2002 ¹³⁵	2.2	1.0 (0.7 to 1.6)	1.9 (1.3 to 2.8)	4.0 (2.3 to 6.9)	4.0 (2.3 to 6.9)
Heart failure admission	Mamdani, 2004 ¹⁵⁵	9.1	1.0 (0.8 to 1.3)	1.8 (1.5 to 2.2)	1.4 (1.0 to 1.9)	1.4 (1.0 to 1.9)

Our results (see Table 11) suggest that in this population, use of celecoxib was neutral with regard to these adverse events when compared with non-use. On the other hand, use of rofecoxib, non-selective NSAIDs, and naproxen would all cause more serious adverse events than they prevented (Table 10). Rofecoxib and naproxen essentially appeared equivalent when

considering all three adverse events together, though rofecoxib was associated with more heart failure admissions and fewer GI bleeds. Our estimates are consistent with analyses of serious adverse events in VIGOR (discussed earlier), which found that rates were essentially equivalent for rofecoxib and non-selective NSAIDs.^{114, 115} However, the result are discordant from analyses of serious adverse events in CLASS, which found that celecoxib offered no advantage over non-selective NSAIDs.^{100, 114} Differences in populations (the Ontario cohort only enrolled patients over 65 years old who filled multiple prescriptions), indications for starting celecoxib, dosing of celecoxib, or co-medication use might account for this discrepancy. In addition, because these studies only included patients who filled multiple prescriptions for NSAIDs, the analyses could underestimate early adverse events.

Table 11. Effects of selective or non-selective NSAIDs on number of serious adverse events

	Estimated effect on MI's (number per 1000 person-years)	Estimated effect on GI bleed (number per 1000 person-years)	Estimated effect on heart failure admissions (number per 1000 person-years)	Net effect on number of MI's, GI bleeds, and heart failure admissions (number per 1000 person-years)
Celecoxib	-0.82 (-2.46 to 1.64)	0 (-0.66 to 1.32)	0 (-1.82 to 2.73)	-0.70 (-3.58 to 2.71)
Rofecoxib	0 (-1.64 to 3.28)	1.98 (0.66 to 3.96)	7.28 (4.55 to 10.92)	9.42 (5.47 to 13.99)
Non-selective NSAIDs	4.1 (1.64 to 6.56)	6.6 (2.86 to 12.98)	3.64 (0 to 8.19)	14.68 (8.59 to 22.72)
Naproxen	0 (-3.28 to 5.74)	6.6 (2.86 to 12.98)	3.64 (0 to 8.19)	10.77 (3.92 to 19.89)

CV and GI safety with valdecoxib

The risk of clinically significant upper GI events (bleeding, perforation, and gastric outlet obstruction) with valdecoxib was evaluated in a manufacturer-funded meta-analysis of eight randomized controlled trials of 12 to 26 weeks duration.¹¹⁸ This study prospectively defined ulcer complications and used independent adjudication to determine adverse events. However, it is not described how assiduously the trials adhered to the adjudication process. Four of the trials were not published, and there was insufficient information about study design to determine the quality of the trials. The meta-analysis found that valdecoxib was associated with a significantly lower rate of significant upper GI events compared with non-selective NSAIDs (0.68% vs. 1.96%, all patients; 0.29% vs. 2.08%, non-aspirin users; $p<0.05$). Another meta-analysis of five trials by the same authors found that valdecoxib was associated with a lower risk of ‘moderate-to-severe’ upper GI symptoms compared with non-specific NSAIDs (HR 0.59, 95% CI 0.47 to 0.74) and similar to placebo.¹⁵⁶ Adverse events were self-reported by patients in these trials, and the quality of the trials was not assessed by the meta-analysts. Two of the included trials were published only in abstract form.

We found no published trials evaluating the risk of cardiovascular events associated with valdecoxib in patients with arthritis. A meta-analysis funded by Pfizer and presented to the FDA in February 2005 analyzed primarily unpublished data from 19 trials of patients with chronic pain (methods described above in the section on celecoxib).¹²² Thirteen studies were of patients with osteoarthritis or rheumatoid arthritis. Three of the trials were longer than 12 weeks in duration.

There was no association between valdecoxib use and either cardiovascular thromboembolic events or myocardial infarction (Table 12). The number of events, however, was low. Only 10

of 4,438 patients (0.2%) randomized to valdecoxib had a cardiovascular event. An earlier meta-analysis of 10 trials (also funded by Pfizer, and using similar methods) also found no difference in risk for myocardial infarction between valdecoxib and either placebo or other NSAIDs.¹²⁸

Table 12. Myocardial infarction in trials of valdecoxib for chronic pain: meta-analysis of 19 trials

Comparison	Risk for myocardial infarction
Valdecoxib \geq 10 mg/day versus placebo	1.80 (0.47-6.97)
Valdecoxib \geq 10 mg/day versus non-selective NSAID	0.32 (0.12-0.87)

Two short term (<2 month) trials in the high-risk setting of post-coronary artery bypass surgery found that parecoxib (an intravenous coxib rapidly converted to valdecoxib) followed by valdecoxib (40 mg bid¹⁵⁷ or 20 mg bid¹⁵⁸) were associated with a two- to three-fold higher risk of cardiovascular events compared with placebo (pooled relative risk 3.08, 95% CI 1.20 to 7.87).¹⁵⁹

FDA information A warning was added to the valdecoxib product label in Nov, 2002. It was prompted by reports of cases of serious anaphylactic reactions and serious dermatologic adverse events in postmarketing surveillance.¹⁶⁰ A study of two large European data sources and the US FDA spontaneous adverse events reporting system prior to the introduction of COX-2 inhibitors found that other NSAIDs—in particular piroxicam and tenoxicam—are also associated with Stevens-Johnson syndrome and toxic epidermal necrolysis.¹⁶¹ However, the rates of these events were extremely low, on the order of one per 100,000 or less during an initial 8-week course of therapy.

GI and CV safety: NSAIDs vs. NSAIDs

Partially selective NSAIDs. Evidence that meloxicam, nabumetone, and etodolac prevent ulcer complications is weaker than that for coxibs. In summary, meloxicam was the most widely studied in short-term trials, meta-analyses, and longer-term observational studies and was generally associated with no advantage in GI protection relative to other partially-selective and non-selective NSAIDs or non-use.^{138, 162-169} More limited evidence for nabumetone and etodolac was insufficient to make reliable judgments about the comparative GI and CV safety.

Meloxicam. Risk of serious ulcer complications alone and/or MI were only found in one controlled clinical trial of meloxicam¹⁶³ and three observational studies.^{138, 164, 166} Rates of GI hemorrhage associated with meloxicam were reported by only one potentially poor-quality controlled clinical trial.¹⁶³ Meloxicam was associated with similar rates of GI hemorrhage at 6 months relative to other NSAIDs (RR 0.32; 95% CI 0.06, 1.63) in 4,526 rheumatoid arthritis patients seen by family or internal medicine physicians in Germany between August 1996 and July 1997.¹⁶³ There is uncertainty about whether the relative risk of GI hemorrhage accounted for the differences in baseline disease severity that favored the control group as it is unclear whether a logistical regression model was applied to the calculation and, if so, which factors were adjusted for.

Estimates of GI and CV risk have also been reported in two recent (2004) cohort studies that followed participants for 14 months,¹⁶⁴ and 2.4 years,¹³⁸ respectively. GI complication-related hospitalizations were similar for meloxicam (0), nabumetone (1, 4.5%), salsalate (1, 5.9%), naproxen (5, 7.9%), and ibuprofen (0) among a cohort of long-term care residents in Indiana (mean age=81.2 years).¹⁶⁴ In a cohort of 59,724 elderly individuals in Quebec, meloxicam (adjusted rate ratio 1.06; 95% CI 0.49, 2.30) and naproxen (1.17; 95% CI 0.75, 1.84) were associated with similar increases in risk of MI relative to non-use.¹³⁸ Meloxicam (RR 1.5; 95%

CI 0.1, 17.1), naproxen (RR 1.0; 95% CI 0.3, 3.3), and piroxicam (RR 0.7; 95% CI 0.2, 2.3) were also all associated with similar nonsignificant risk of MI relative to diclofenac as reported by a nested case-control study using data from the UK GPRD.¹⁶⁶

Estimates of GI risk using a composite outcome of minor (GI tolerability) and major (PUBs, hospitalization or related death) were reported in one good-quality meta-analysis.¹⁶⁷ The risk of GI complications for meloxicam relative to the summary estimate from all RCTs (RR 1.24; 95% CI 0.98, 1.56) was comparable with that of the non-selective NSAIDs included in the meta-regression model. Relative risks of GI hospitalizations or related-deaths alone were not reported. Composite GI outcome data from cohort studies was also analyzed and found to provide higher risk estimates (combined NSAID RR 2.2, 95% CI 1.7, 2.9) than those from the trials, but the results were not stratified by individual NSAID.

Three meta-analyses focused only on short-term trials that reported PUB (defined as perforation, symptomatic ulcer, or bleeding) for meloxicam. The first meta-analysis included 10 trials (seven double-blinded).¹⁶⁵ Most of the patients were followed for only 4 weeks. The meta-analysis did not report absolute event rates, but found that the risk of PUB was reduced in the meloxicam patients (OR 0.52, 95% CI 0.28-0.96). Another double-blind trial of meloxicam 7.5, 15 and 22.5 mg and diclofenac 75 mg bid reporting 12-week PUB rates in RA patients (n=894) has been published since the Schoenfeld meta-analysis.¹⁶² PUB rates of 1.1%, 0.5%, 0.6% and 0% were not significantly different between meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid. There was a dose-response relationship between meloxicam and PUB rates in a more recent meta-analysis funded by the makers of meloxicam in which endpoints were ascertained by a blinded, external adjudication committee using manufacturer-held documents from 28 unidentified trials.¹⁷⁰ Meloxicam was associated with lower PUB rates during the first 60 days than diclofenac, piroxicam, or naproxen, respectively, at 7.5mg, but the 15 mg dose was only associated with lower PUB rates than piroxicam. In a third meta-analysis of three short-term (4- to 6-week) trials, which has not yet been published, there was no difference in the risk of complicated ulcers (perforations, obstructions and bleeds) associated with meloxicam relative to piroxicam (two trials^{44,49}) or diclofenac (one trial¹⁷¹) when the trials were pooled (Relative Risk 0.50; 95% CI 0.23, 1.12).¹¹⁷

Nabumetone. For nabumetone, a fair-quality meta-analysis of six short-term (3 to 6 months) studies (five published and one abstract) found one PUB event among 4,098 patients taking nabumetone versus 17 events among 1,874 non-selective NSAID patients; this result was highly statistically significant.¹⁷² The absolute PUB rates were about 2 versus 6 per 1,000 patient-years. For comparison, in a similar meta-analysis of rofecoxib studies, the PUB rates per 1,000 patients per year were 13 for rofecoxib and 26 for NSAIDs.¹¹⁹ There was also a significant reduction in treatment-related hospitalizations in the nabumetone group (6.4 per 1,000 patients per year vs. 20.3 per 1,000 patients per year). The results of this meta-analysis are not directly comparable to other trials and meta-analyses that reported complicated ulcers as a separate outcome because symptomatic ulcers were also included. In addition, the methods used to ascertain the endpoints in the trials were not described in enough detail to determine whether they were accurate and applied consistently. Finally, the similarity of the subjects in the efficacy trials to a broader group of NSAID users was not addressed.

Etodolac. Studies of serious GI bleeding risk alone were not found for etodolac. Clear GI protective effects were not evident for etodolac relative to non-use¹⁶⁸ or relative to naproxen¹⁷³ in two retrospective database studies that reported PUB rates. Analyses of medical information ascertained from a blinded review of the UK General Practice Database revealed that adjusted

relative risks of PUB compared with non-use ranged from 2.2 (95% CI 0.4, 11.3) for etodolac to 6.2 (95% CI 3.7, 10.1) for piroxicam and were comparable across all NSAIDs studied.¹⁷⁴ When directly compared with naproxen using historical data from Dallas Veterans Affairs Medical Center records, etodolac had a GI protective effect for all users (RR 0.24 (95% CI 0.09, 0.63)) and for NSAID-naïve users (RR 0.18 (95% CI 0.05, 0.61)) only when low-dose aspirin was not taken concomitantly.¹⁷³

Non-selective NSAIDs - GI safety. Randomized controlled trials¹¹⁷ and observational studies^{175, 176} consistently report that non-selective, non-aspirin NSAIDs are associated with increased risks of serious GI events relative to non-use. There is no clear, consistent evidence that any one non-selective, non-aspirin NSAID is any less risky than another.

Preliminary results from a meta-analysis of randomized controlled trials found that selective COX-2 inhibitors as a class (defined by the investigators as celecoxib, rofecoxib, valdecoxib, lumiracoxib, and meloxicam) were associated with lower risks of complicated ulcers (perforation, obstruction, or bleed) when compared with naproxen (0.34; 95% CI 0.24, 0.48), ibuprofen (0.46; 95% CI 0.30, 0.70), and diclofenac (0.31; 95% CI 0.06, 1.61).¹¹⁷ There were no clear differences among the three non-selective NSAIDs. The validity of these findings cannot be assessed until the full report is published. However, they are consistent with results from a previous meta-analysis in which increases in risk of GI complications (major plus minor) were similar for different NSAIDs relative to non-use: indomethacin (RR 2.25; 95% CI 1.01, 5.07), naproxen (RR 1.83; 95% CI 1.25, 2.68), diclofenac (RR 1.73; 95% CI 1.21, 2.46), piroxicam (RR 1.66; 95% CI 1.14, 2.44), tenoxicam (RR 1.43; 95% CI 0.40, 5.14), meloxicam (RR 1.24; 95% CI 0.98, 1.56) and ibuprofen (RR 1.19; 95% CI 0.93, 1.54).¹⁶⁷

In an earlier, collaborative meta-analysis of cohort and case-control studies published between 1985 and 1994, use of all non-selective NSAIDs were associated with significantly increased risk of peptic ulcer complication hospitalizations relative to non-use.¹⁷⁵ Ibuprofen, at doses used in general practice, was associated with the lowest risk of peptic ulcer complication hospitalizations.¹⁷⁵ Risk of serious GI event-related hospitalizations and specialist visits was dose-dependent, however, and was no lower for ibuprofen relative to non-use at low-medium (RR 2.1, 95% CI 1.6, 2.7) and high doses (RR 5.5, 95% CI 3.0, 10.0) than for any other non-aspirin, non-selective NSAID in a subsequent meta-analysis of cohort and case-control studies published from 1990-1999 (Table 13).^{168, 176}

Table 13. Relative Risk (95% CI) of UGIB* for NSAIDs vs. non-use

NSAID	Overall	Hernandez-Diaz 2000 ¹⁷⁶		Garcia-Rodriguez 2001 ¹⁶⁸
		Dose		Overall
		Low-Medium	High	
Diclofenac	3.3 (2.8, 3.9)	3.1 (2.0, 4.7)	3.6 (2.3, 5.6)	4.6 (3.6, 5.8)
Ibuprofen	1.9 (1.6, 2.2)	2.1 (1.6, 2.7)	5.5 (3.0, 10.0)	2.5 (1.9, 3.4)
Indomethacin	4.6 (3.8, 5.5)	3.0 (2.2, 4.2)	6.5 (4.8, 8.6)	5.2 (3.2, 8.3)
Ketoprofen	4.6 (3.3, 6.4)	NR	NR	3.3 (1.9, 5.9)
Naproxen	4.0 (3.5, 4.6)	3.5 (2.8, 4.3)	5.1 (3.8, 6.9)	4.0 (2.8, 5.8)
Piroxicam	6.3 (5.5, 7.2)	5.6 (4.7, 6.7)	6.2 (4.4, 8.7)	6.2 (3.7, 10.1)
Sulindac	3.6 (2.8, 4.7)	NR	NR	NR

*Upper GI tract bleeding/perforation

Non-selective NSAIDs were also associated with increased risk of serious GI events relative to non-use in more recent observational studies. Ibuprofen (Odds Ratio 1.42, 95% CI 1.27, 1.59), diclofenac (OR 1.96; 95% CI 1.78, 2.15) and naproxen (OR 2.12, 95% CI 1.73, 2.15) were

all associated with increased risk of GI hemorrhage, perforation, surgery or undefined uncomplicated events relative to non-use in a case-control study of the UK General Practice Research Database.¹³⁴ Risk estimates (odds ratios; 95% CI) of upper GI events resulting in hospitalization associated with NSAIDs relative to non-use ranged from 3.1 (2.0, 4.9) for ibuprofen to 24.7 (8.0, 77.0) for ketorolac when based on data from 10 hospitals in Spain using a case-control design.¹³⁷

Non-selective NSAIDs – CV safety. Evidence regarding the comparative risk of serious CV events for non-selective NSAIDs is more limited than the evidence for selective COX-2 inhibitors. In particular, large, long-term clinical trials evaluating the risk of MI or other cardiovascular events are lacking. Preliminary results (not yet published or available for critical review) from a systematic review of 138 randomized controlled trials of at least 4 weeks duration with more than 144,000 participants, however, has been presented to the Health Canada Expert Advisory Panel and were recently summarized.¹¹⁶ Many of the estimates of cardiovascular risk in this analysis were obtained by requesting unpublished data from trial sponsors. The systematic review found that the risk of clinically important cardiovascular events was increased to a similar degree in patients treated with selective COX-2 inhibitors and non-naproxen NSAIDs when compared with placebo or naproxen. The absolute increase in cardiovascular risk for selective COX-2 inhibitors and non-naproxen NSAIDs was similar at approximately 0.3% per year. On the other hand, in December 2004, the Alzheimer’s Disease Anti-Inflammatory Prevention Trial (ADAPT) was suspended in part because of an “apparent increase in cardiovascular and cerebrovascular events among the participants taking naproxen when compared with those on placebo.”¹³⁰ However, further details from the ADAPT trial have not yet become available.

Naproxen. The risk of MI and other cardiovascular events associated with various non-selective NSAIDs has been evaluated in numerous observational studies. Naproxen has been the most extensively studied non-selective NSAID because of interest generated after the results of the VIGOR trial were published. In order to assess the proposed hypothesis that naproxen is protective against myocardial infarction (rather than rofecoxib causing additional myocardial infarctions), authors of a meta-analysis of randomized controlled trials of rofecoxib also analyzed 11 observational studies of naproxen (four based on the General Practice Research Database).¹²⁵ Compared with non-naproxen NSAIDs, naproxen was associated with a small cardioprotective effect (OR 0.86, 95% CI 0.75 to 0.99). The modest cardioprotective effect could not explain the 80% reduction in risk with naproxen compared with rofecoxib observed in the VIGOR trial. In addition, meta-regression analyses indicated that the funding source largely explained between-study heterogeneity. Specifically, Merck-funded studies of naproxen reported larger cardioprotective effects. An FDA review of four observational studies of naproxen that found a cardioprotective effect identified several issues in the design, analysis, or results that affected the interpretation of these findings.¹⁴³ In a study by Rahme and colleagues, current exposure to naproxen was associated with a lower risk of acute MI compared with exposure to other NSAIDs (OR 0.79, 95% CI 0.63 to 0.99).¹⁷⁷ However, when the FDA reviewer re-analyzed the data to compare current exposure to naproxen to non-use of NSAIDs, naproxen was associated with a *higher* risk (OR 1.28, 95% CI 1.10 to 1.49).¹⁴³ Although the FDA re-analysis was not adjusted for confounders, examination of point estimates in the paper suggests that the effects of adjusting would be minor. A study by Kimmel and colleagues found that naproxen was associated with a lower risk of MI compared with non-use (OR 0.48, 95% CI

0.28 to 0.82), but the results were susceptible to participation bias (about 50% of cases and controls participated) and recall bias (exposure determined by telephone interviews rather than by using pharmaceutical databases or other sources).¹⁷⁸ The third study, by Watson and colleagues, reported a lower risk of thromboembolic cardiovascular events with current use of naproxen versus non-use (OR 0.61, 95% CI 0.39 to 0.94), but did not adequately control for baseline cardiovascular risk.¹⁷⁹ Further, when the endpoint of MI alone rather than the composite endpoint of thromboembolic cardiovascular events (which included subdural hematoma, subarachnoid hemorrhage, ischemic stroke, sudden death, or MI) was evaluated, the reduction in risk was not significant (OR 0.57, 95% CI 0.31 to 1.06). Finally, a study by Solomon and colleagues reported a lower risk of MI with use of naproxen within 6 months of an acute MI (OR 0.84, 95% CI 0.72 to 0.98).¹⁸⁰ However, the risk was reduced to a similar degree when the naproxen prescription had run out between 61 and 180 days earlier. Unless naproxen exerts a long-term cardioprotective effect (which is thought to be highly unlikely), these findings are suggestive of underlying selection bias—in other words, persons receiving naproxen were at lower risk for cardiovascular events, and adjustment for known confounders did not eliminate this bias.

In three other recent observational studies (not included in the Juni systematic review) evaluating cardiovascular risk, naproxen was not associated with a cardioprotective effect (Table 14).^{138, 141, 144, 152} However, naproxen was also not clearly associated with an increased risk of myocardial infarction. None of these studies received pharmaceutical industry funding. The FDA review also included two other unpublished studies (Ingenix and MediCal studies) that found no cardioprotective benefit associated with naproxen.¹⁴³

Table 14. Risk of myocardial infarction associated with naproxen in recent observational studies not included in the Juni meta-analysis

Study	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴¹	1.27 (1.01 to 1.60)
Levesque, 2005 ¹³⁸	1.17 (0.75 to 1.84)
Johnsen, 2005 ¹⁴⁴	1.50 (0.99 to 2.29)

Results from observational studies regarding the cardiovascular risk associated with non-naproxen, non-selective NSAIDs are mixed. Non-selective NSAIDs as a class and individual NSAIDs have not been consistently associated with increased risks. Results from recent observational studies from the COX-2 era are summarized in Table 15.

Table 15. Risk of myocardial infarction associated with non-selective, non-naproxen NSAIDs

Study	Drug	Estimate of risk (current use versus no or remote use)
Hippisley-Cox, 2005 ¹⁴¹	Ibuprofen	1.24 (1.11 to 1.39)
	Diclofenac	1.55 (1.39 to 1.72)
	Other non-selective, non-naproxen NSAIDs	1.21 (1.02 to 1.44)
Graham, 2005 ¹⁵²	Non-selective, non-naproxen NSAIDs	1.13 (1.01 to 1.27)
Levesque, 2005 ¹³⁸	Non-selective, non-naproxen NSAIDs	1.00 (0.73 to 1.37)
Johnsen, 2005 ¹⁴⁴	Non-selective, non-naproxen NSAIDs	1.50 (0.99 to 2.29)
Garcia Rodriguez, 2004 ¹⁶⁹	Ibuprofen	1.06 (0.87 to 1.29)
	Diclofenac	1.18 (0.99 to 1.40)
	Ketoprofen	1.08 (0.59 to 1.96)
	Piroxicam	1.25 (0.69 to 2.25)

	Indomethacin	0.86 (0.56 to 1.32)
	Other non-selective, non-naproxen NSAIDs	0.89 (0.63 to 1.25)
Mamdani, 2003 ¹⁴²	Non-selective, non-naproxen NSAIDs	1.2 (0.9 to 1.4)
Ray, 2002 ¹⁴⁶	Ibuprofen	0.91 (0.78 to 1.06)
Solomon, 2002 ¹⁸⁰	Ibuprofen	1.02 (0.88 to 1.18)
Watson, 2002 ¹⁷⁹	Ibuprofen	0.74 (0.35 to 1.55)
	Diclofenac	1.68 (1.14 to 2.49)

In April 2005, the FDA issued a Public Health Advisory stating, “Long-term controlled clinical trials have not been conducted with most of these (non-selective) NSAIDs. However, the available data suggest that use of these drugs may increase CV risk. It is very difficult to draw conclusions about the relative CV risk among the COX-2 selective and non-selective NSAIDs with the data available. All sponsors of non-selective NSAIDs will be asked to conduct and submit to FDA a comprehensive review and analysis of available controlled clinical trial databases pertaining to their NSAID product(s) to which they have access to further evaluate the potential for increased CV risk.”¹⁸¹ The FDA also required labeling changes to both prescription and non-prescription non-selective NSAIDs warning about potential cardiovascular risks.

Aspirin. Randomized controlled trials¹⁸² and observational studies consistently report that aspirin increases risk of serious GI events relative to placebo or non-use,^{134, 175, 182} but at a rate similar to that of other non-selective NSAIDs.^{134, 174, 175} Randomized controlled trials assessing the risk of upper GI bleeding with aspirin have mainly been conducted in populations receiving aspirin as prophylaxis for thrombotic events. In addition to being at higher cardiovascular risk, the populations evaluated in these trials may also differ in other important ways from patients who take aspirin for arthritis. In these studies, the dose of aspirin varied widely and was lower (50 mg to 1500 mg daily) than considered effective for analgesia and anti-inflammatory effects, and patients typically received aspirin for prolonged periods. In a good-quality meta-analysis of 24 randomized trials with nearly 66,000 participants, the risk of gastrointestinal hemorrhage was 2.47% with aspirin compared with 1.42% with placebo (OR 1.68, 95% CI 1.51 to 1.88), based on an average of 28 months therapy.¹⁸² There was no relation between gastrointestinal hemorrhage and dose in this study. Further, modified release formulations did not attenuate the risk for bleeding. Systematic reviews of cohort and case-control studies published between 1985 and 2001 reported similar findings,^{174, 175} except that the most recent review found a dose-response relationship between aspirin and risk of bleeding.¹⁷⁴ However, aspirin was associated with upper GI bleeding even at low doses. Findings from a more recent UK practice-based case-control study (9,407 cases) found that compared with non-use, aspirin was associated with an increase in the risk of complicated or uncomplicated adverse GI events (odds ratio 1.60, 95% CI 1.49, 1.72) similar to that of naproxen, diclofenac, and ibuprofen.¹³⁴ Findings from this case-control study are consistent with a systematic review of observational studies that only assessed peptic ulcer-related hospitalizations.¹⁷⁵

Aspirin is also known to be protective against occlusive vascular events because of its antiplatelet effects. In a collaborative meta-analysis of 65 randomized controlled trials of aspirin for prophylaxis against thrombotic events, any dose of aspirin reduced the risk of vascular events by an average of 23% (standard error 2).¹⁸³ The cardioprotective effects of aspirin appeared lower (13%) in three trials evaluating doses of lower than 75 mg/day, but in trials that directly compared higher and lower doses, there were no significant differences. Again, the populations evaluated in these trials probably varied substantially from trials of patients with arthritis.

Salsalate. Limited evidence from flawed observational studies with small sample sizes is insufficient to make any strong conclusions about the GI safety profile of salsalate relative to other NSAIDs. The GI safety profile of salsalate has been primarily evaluated in the general rheumatoid arthritis population using the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) databases that reported the “Toxicity Index”—a broad composite endpoint involving symptoms from all body systems, laboratory abnormalities, and all-cause hospitalizations.¹⁸⁴⁻¹⁸⁷ Bodily symptoms were collected every 6 months using patient self-report in response to open-ended questions (e.g., Did you have any medication side effects? If so, to what drugs? Was the side effect mild, moderate, or severe?). Hospitalization and death data were ascertained from discharge summaries and death certificates, and methods of laboratory abnormality data ascertainment are unclear. Descriptions of study methods varied, but in general the ARAMIS studies were vague with regard to patient-selection methods and ascertainment methods; adverse events were not prespecified; exposure duration and length of follow-up were unclear; and adjustments were made only for demographic factors such as age and gender. Because the overall design of these studies is generally of lower quality and more subject to recall bias than studies that use administrative or practice-based databases to ascertain exposures and outcomes, the findings that aspirin, salsalate, and ibuprofen were the least toxic among the NSAIDs studied (Table 16 below) are less convincing than in more recent observational studies that evaluated the risk associated with COX-2 inhibitors (discussed above).

Table 16. Toxicity Index Scores from ARAMIS database studies

Study	Aspirin	Ibuprofen	Salsalate	Others (range)
Fries 1991 ¹⁸⁴	1.19	1.94	1.28	2.17 (Naproxen) to 3.99 (Indomethacin)
Fries 1993 ¹⁸⁶	1.33	1.89	NR	1.90 (Naproxen) to 2.86 (Tolmetin)
Fries 1996 ¹⁸⁵	1.77	2.68	2.00	1.63 (Sulindac) to 3.09 (Ketoprofen)
Singh 1997 ¹⁸⁷	2.25	1.95	1.79	3.29 (Naproxen) to 5.14 (Meclofenamate)

One ARAMIS database study assessed a more stringent outcome, but otherwise suffered from the same flaws described above.¹⁸⁷ This study found that aspirin is associated with a greater risk of GI bleeds and other clinically significant GI events requiring hospitalization than paracetamol (RR 4.14; 95% CI not reported; $p < 0.01$). Serious GI event rates associated with salsalate were also evaluated in one cohort of long-term care residents in Indiana that found that the number of cases of salsalate-related GI complication hospitalizations (1, 5.9%) after 14 months was similar to that of other selective and non-selective NSAIDs (cited in partially selective NSAID section above).¹⁶⁴

Other adverse events associated with selective and non-selective NSAIDs

Mortality. Large clinical trials have not shown differences in mortality rates between different NSAIDs. In VIGOR, for example, mortality was 0.5% with rofecoxib versus 0.4% with naproxen,¹⁸ and in CLASS mortality rates were 0.47%, 0.37%, and 0.45% for celecoxib, diclofenac, and ibuprofen, respectively.¹⁰⁰ A meta-analysis of unpublished company clinical trial reports (including CLASS) found no significant difference in rates of death in patients randomized to celecoxib compared with non-selective NSAIDs, though there were few events (0.03% or 6/18,325 in the celecoxib arms versus 0.11% or 14/12,685 in the NSAID arms).⁶⁶ In one retrospective cohort study of Saskatchewan health-services databases that followed patients from 6 months following prescription until death, nabumetone was associated with significantly

lower rates of all-cause mortality compared with diclofenac (adjusted odds ratio 1.96; 95% CI 1.25, 3.07) and naproxen (adjusted odds ratio 2.95, 95% CI 1.88, 4.62).¹⁸⁸ However, we found no other studies that replicated this finding.

Hypertension, CHF, edema, and renal function. All non-selective NSAIDs appear to be associated with increases in blood pressure. However, evidence regarding differential effects of specific NSAIDs is somewhat conflicting. Two meta-analyses of placebo-controlled trials have compared the effects of different non-selective NSAIDs on blood pressure increases.^{189, 190} One meta-analysis found that non-selective NSAIDs raise mean blood pressure by an average of about 5.0 mm Hg (95% CI, 95% CI 1.2 to 8.7).¹⁸⁹ In both meta-analyses, aspirin and sulindac were associated with minimal hypertensive affect. The 2nd meta-analysis found that piroxicam and ibuprofen had negligible effects on blood pressure, and that indomethacin and naproxen were associated with the largest increases.¹⁹⁰ By contrast, the other found that piroxicam produced the most marked elevation in blood pressure.¹⁸⁹ In an analysis of head-to-head trials, there were no significant differences between indomethacin and sulindac (10 trials), indomethacin and salicylate (one trial), diclofenac and sulindac (one trial), ibuprofen and sulindac (one trial), and naproxen and sulindac (three trials).¹⁸⁹ The reliability of these results is compromised by a high likelihood of publication bias; more than half of published NSAID trials did not report hypertension rates as an outcome.¹⁹⁰

Several studies have reported hypertension outcomes for selective COX-2 inhibitors compared to non-selective NSAIDs. Evidence on differential effects on blood pressure is inconclusive because of dissimilarities in dosing and comparator drugs, and a high probability of publication bias. In the VIGOR trial, rofecoxib 50 mg daily was associated with a higher risk of discontinuation due to hypertension-related adverse events than naproxen (RR 4.67, 95% CI 1.93 to 11.28).¹¹⁵ In addition, 19 patients developed CHF-related adverse events during 4,047 patient-years of exposure, compared with nine patients during 4,029 patient-years of exposure to naproxen (RR 2.11, 95% CI 0.96 to 4.67). By contrast, another large trial (N=5557) of rofecoxib 25 mg daily versus naproxen (ADVANTAGE) found no significant differences for hypertension (2.9% vs. 2.4%), discontinuations due to hypertension (0.5% vs. 0.2%), and edema; heart failure rates were not reported.⁸⁰ The discrepancy between ADVANTAGE and VIGOR suggests that the risk of developing hypertension-related adverse events is dose-related.

A good-quality Cochrane review found that rates of edema and hypertension were not reported in most trials of rofecoxib versus a non-selective NSAID.⁸² For rofecoxib versus nabumetone, there was no difference in the rate of hypertension in two trials (pooled RR 1.46, 95% CI 0.53 to 4.12). A meta-analysis of nine phase IIb/III osteoarthritis trials sponsored by the manufacturer of rofecoxib published in 2001 found that rofecoxib 12.5 mg and 25 mg daily were associated with higher rates of lower extremity edema, congestive heart failure, and hypertension than placebo.¹⁹¹ Edema and hypertension rates were similar between the rofecoxib (1.2 per 100 patient-months) and ibuprofen (1.3 per 100 patient-months) groups but somewhat higher than in the diclofenac group (0.3 per 100 patient months). Discontinuations due to these adverse events were rare: of 2,829 randomized to rofecoxib, seven discontinued due to edema, two due to hypertension, and one due to CHF. However, five of the nine trials were shorter than 6 weeks in duration, so these rates are not likely to be representative of results in long-term users. In the long-term APPROVe polyp prevention trial, hypertension (RR 2.02, 95% CI 1.71 to 2.38), edema (RR 1.57, 95% CI 1.17 to 2.10), and heart failure or pulmonary edema (RR 4.61, 95% CI 1.50 to 18.83) were all increased in the rofecoxib arm compared with placebo.¹⁹²

In CLASS, celecoxib was associated with a similar rate of hypertension (new-onset and

aggravated pre-existing) compared with diclofenac (2.7% vs. 2.6%), but a significantly lower rate than ibuprofen (2.7% vs. 4.2%).¹¹¹ CHF rates were similar in patients randomized to celecoxib versus either ibuprofen or diclofenac (0.3% vs. 0.3%). A Pfizer-funded meta-analysis submitted to the FDA found that, for celecoxib (any dose), the risk of developing hypertension was higher than placebo (1.1% vs. 0.7%, $p=0.023$) but lower than the non-selective NSAIDs (1.5% vs. 2.0%, $p=0.002$).¹²² Heart failure was more frequent in patients taking celecoxib than those taking placebo (13 of 8,405 versus one of 4,057, $p=0.046$), though not compared with non-selective NSAIDs (0.1% vs. 0.2%, $p=0.056$). Like the rofecoxib meta-analysis, most of these studies were short-term and there was no information about the quality of the trials. A second meta-analysis, funded by Pfizer and the Oxford Pain Relief Trust, also analyzed unpublished data unavailable to the public had similar findings (celecoxib vs. placebo RR 0.70, 95% CI 0.43 to 1.1).⁶⁶ Results of the APC polyp prevention trial found no difference in rates of heart failure, stroke, or other thromboembolic events between patients randomized to celecoxib versus those randomized to placebo, though event rates were low (five cases of heart failure, eight strokes, and seven thromboembolic events among 1,356 subjects).¹²⁹

Evidence on the comparative blood pressure effects of celecoxib compared to rofecoxib are also difficult to interpret. A good-quality Cochrane review found no difference in rates of clinically significant increases in blood pressure or edema associated with rofecoxib versus celecoxib in three head-to-head trials of average-risk populations with osteoarthritis.⁸² Another meta-analysis of unpublished clinical trial data also found no difference in risk of hypertension or aggravated hypertension in patients on celecoxib versus rofecoxib (RR 0.75, 95% CI 0.52 to 1.1).⁶⁶ On the other hand, in contrast to the Cochrane review, the analysis of company clinical trial reports found a lower rate of edema with celecoxib versus rofecoxib (5 trials, RR 0.72, 95% CI 0.62 to 0.83). Three short-term head-to-head trials of celecoxib and rofecoxib funded by the manufacturer of celecoxib have also examined their relative effects on edema and blood pressure in higher-risk populations of hypertensive, osteoarthritic patients.^{89, 94, 193} The results of these trials must be interpreted cautiously because they evaluated doses (rofecoxib 25 mg daily and celecoxib 200 mg daily) that may not provide equivalent pain relief. Two 6-week trials of elderly (>65 years) patients with osteoarthritis and on antihypertensive therapy (SUCCESS VI and SUCCESS VII) found that rates of increased systolic blood pressure (>20 mm Hg increase and absolute value >140 mm Hg) were higher in patients randomized to rofecoxib compared to celecoxib: 14.9% vs. 6.9% ($p<0.01$) in one trial⁹⁴ and 17% vs. 11% ($p=0.032$) in the other.⁸⁹ However, in one of these trials (SUCCESS VI),⁸⁹ there was an important baseline difference in the proportion of patients who took an ACE inhibitor for hypertension (40% for celecoxib-treated patients versus 29% for rofecoxib-treated patients, $p=0.002$). Although not statistically significant, fewer celecoxib-treatment patients had angina (16.3% vs. 19.8%) or a history of myocardial infarction (8% vs. 9.3%). These differences cast doubt on the quality of the trial: successful randomization is unlikely to have resulted in such marked apparent baseline differences. In the third trial (CRESCENT), which enrolled patients with controlled hypertension, diabetes, and osteoarthritis, the proportion that developed ambulatory hypertension (systolic blood pressure >135) was higher with rofecoxib than with celecoxib (30% vs. 16%, $p=0.05$).¹⁹³ In the CRESCENT and SUCCESS-VI trials, edema was more common in patients assigned to rofecoxib compared with those assigned to celecoxib (7.7% vs. 4.7%, $p<0.05$ ¹⁹³ and 9.5% vs. 4.9%, $p=0.014$ ⁸⁹). Three patients on rofecoxib and two on celecoxib developed heart failure in CRESCENT compared with four versus none in SUCCESS-VI; these differences were not significant. Discontinuations due to these adverse events did not differ.

With regards to renal toxicity, there is little evidence to suggest that selective NSAIDs as a class are safer than non-selective NSAIDs with regards to renal toxicity. A systematic review of five small (sample size range 15 to 67), short-term (28 days or less) trials found that selective NSAIDs had similar effects on glomerular filtration rate and creatinine clearance in three trials, and were modestly superior in two.¹⁹⁴ The clinical effects of the modest differences observed in the latter two trials are unclear.

There is also no clear evidence suggesting that celecoxib is associated with improved renal safety compared with rofecoxib. In the CLASS trial, there was one fewer episode of edema, hypertension, or increased creatinine for every 62 patients treated with celecoxib instead of ibuprofen 800mg tid or diclofenac 75 bid.⁵⁷ The effects of celecoxib on renal function were also reviewed in a meta-analysis of primarily unpublished data (not including CLASS) that found that the overall incidence of renal adverse events was similar to that of non-selective NSAIDs.¹⁹⁵ A more recent meta-analysis funded by the manufacturer of celecoxib that included CLASS reported similar findings (RR for raised creatinine >1.3 times the upper limit of normal 0.78, 95% CI 0.46 to 1.3).⁶⁶ In VIGOR, the incidence of adverse events related to renal function (outcome not specifically defined) was similar for the rofecoxib and naproxen groups (1.2% versus 0.9%), with 0.2% discontinuing treatment in each arm because of these events.¹⁸ A meta-analysis of manufacturer's data found that rofecoxib was associated with an overall incidence of elevations in serum creatinine similar to non-selective NSAIDs.¹⁹¹ Discontinuations due to elevated serum creatinine were rare, and there were no cases of acute renal failure (not defined) associated with rofecoxib.

The risks of hypertension and heart failure with rofecoxib and celecoxib have been evaluated in several good-quality observational studies. A large case-control study found that rofecoxib users were at significantly increased risk for new-onset hypertension compared with patients taking celecoxib (OR 1.6, 95% CI 1.2 to 2.1).¹⁹⁶ A retrospective cohort study found that rofecoxib was associated with an increased risk of admission for heart failure compared with NSAID –non-users (RR 1.8, 95% CI 1.5 to 2.2), though celecoxib was not (RR 1.0, 95% CI 0.8 to 1.3).¹⁵⁵ Rofecoxib (HR 1.27, 95% CI 1.09 to 1.49) and non-selective NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) were also associated with higher risks of death or recurrent CHF compared with celecoxib in another study of high-risk patients following a heart-failure admission.¹⁹⁷ In two observational studies, use of non-selective NSAIDs was associated with heart-failure admissions (RR 1.4, 95% CI 1.0 to 1.9)¹⁵⁵ and newly diagnosed heart failure (adjusted RR 1.6, 95% CI 1.2 to 2.1)¹⁹⁸ when compared with non-use.

Hepatotoxicity. We identified one systematic review that evaluated rates of aminotransferase elevations, liver-related discontinuations, and other serious hepatic adverse events, including hospitalizations and deaths, in randomized controlled trials of rofecoxib, celecoxib, valdecoxib, meloxicam, diclofenac, naproxen, and ibuprofen in adults with osteoarthritis or rheumatoid arthritis.¹⁹⁹ It identified 67 published articles and 65 studies accessible from the FDA archives. Diclofenac (3.55%, 95% CI 3.12% to 4.03%) and rofecoxib (1.80%, 95% CI 1.52% to 2.13%) had higher rates of aminotransferase elevations >3 times the upper limit of normal compared with placebo (0.29%; 95% CI 0.17% to 0.51%) and the other NSAIDs (all < or = 0.43%). However, only diclofenac was associated with a higher rate of liver-related discontinuations than placebo (2.17%, 95% CI 1.78% to 2.64%). Serious complications related to liver toxicity were extremely rare: only one liver-related hospitalization (among 37,671 patients) and death (among 51,942 patients) occurred in a patient on naproxen in the

VIGOR trial.

A recent systematic review of seven population-based epidemiological studies of hepatotoxicity with NSAIDs found a similarly low risk of serious hepatic toxicity.²⁰⁰ In those studies, the excess risk of liver injury associated with current NSAIDs ranged from 4.8 to 8.6/100,000 person-years of exposure compared with past use. There were zero deaths from liver injury associated with NSAIDs in over 396,392 patient-years of exposure. A recent cohort study from Italy found that nimesulide, an NSAID not available in the U.S., was associated with a higher incidence of serious liver injury compared with other NSAIDs.²⁰¹ None of the other NSAIDs, including celecoxib, were associated with an increased risk of serious liver injury. An earlier review of five population-based studies found that sulindac was associated with a 5-10 fold higher incidence of hepatic injury compared with other NSAIDs.²⁰² Diclofenac was associated with higher rates of aminotransferase elevations compared with users of other NSAIDs, but not with a higher incidence of serious liver disease.

Tolerability

NSAID vs. NSAID.

Partially selective NSAIDs. There is some evidence that meloxicam (7.5mg or 15mg) is better tolerated than non-selective NSAIDs. The meta-analysis of meloxicam studies mentioned earlier found lower rates of any gastrointestinal event (OR 0.64; 95% CI 0.59, 0.69) and withdrawals due to GI events (OR 0.59; 95% CI 0.52, 0.67) compared with NSAIDs, but as mentioned before it included some inadequately blinded studies; only blinded studies are reliable for assessing withdrawals and attributing the cause of adverse events.¹⁶⁵ The double-blind trial of meloxicam 7.5, 15, and 22.5 mg and diclofenac 75 mg bid mentioned earlier²⁰³ found no significant differences among the treatments in rates of withdrawals due to adverse events or in incidence of overall and gastrointestinal tolerability.

In the nabumetone meta-analysis, the incidence of GI adverse events was significantly different (25.3% vs. 28.2%, $p=.007$), corresponding to about one fewer event for every 34 patients treated with nabumetone.¹⁷²

Gastrointestinal effects of etodolac were evaluated in numerous randomized controlled trials and literature reviews that reported microbleeding and/or endoscopic outcomes. No systematic review of the overall clinical tolerability profile of etodolac relative to non-selective outcomes has yet been found, however.

Non-selective NSAIDs. One Cochrane review evaluated the tolerability of different NSAIDs.³⁸ The only relatively consistent finding was that indomethacin was associated with higher rates of toxicity than other NSAIDs, but it was not clear if these differences were statistically significant.

Aspirin and salsalate. Five randomized trials have evaluated the efficacy or safety of aspirin or salsalate compared with non-aspirin NSAIDs in patients with arthritis.^{53, 204-207} All were short-term in duration (≤ 12 weeks) and involved a total of 471 patients; of the subjects enrolled, only four had osteoarthritis of the hip/knee for every 100 patients with rheumatoid arthritis. Aspirin was associated with higher incidence of overall adverse events than salsalate (70% vs. 40%, $p<0.05$)⁵³ and diclofenac (61% vs. 46%; $p<0.05$) and these led to higher rates of withdrawals due to adverse events for aspirin compared with diclofenac (23% vs. 6%; $p<0.05$).²⁰⁴ Higher incidence of overall adverse events were described for salsalate when compared with other non-selective NSAIDs in two^{206, 207} of three trials; but, rates were not reported.

COX-2 vs. NSAID.

Celecoxib was consistently associated with a more favorable overall and GI tolerability profile relative to some, but not all, non-selective NSAIDs in short-term RCTs of patients with OA/RA as reported in two manufacturer-funded meta-analyses^{65, 66} and one good-quality Cochrane review (Table 17).²⁰⁸ Evidence of relative tolerability is less consistent for the comparisons of rofecoxib to partially-selective and non-selective NSAIDs in short-term RCTs of patients with OA/RA as reported in one manufacturer-funded meta-analysis²⁰⁹ and two good-quality Cochrane reviews.^{82, 83}

Effect size differences between the COX-2 manufacturer-funded analyses and the Cochrane reviews may have been due, in large part, to differences in methods of study selection and statistical analyses. The Cochrane Reviews primarily relied upon electronic database searches for identification of published RCTs involving narrow patient populations, and results from each trial were generally presented separately.^{82, 83, 208} Manufacturer-funded meta-analyses relied solely^{66, 209} or in part⁶⁵ on their internal data as the primary search method and presented pooled relative-risk estimates using data from published and unpublished RCTs of broader populations with both OA and RA patients.

Table 17. Tolerability profile of COX-2's vs. NSAIDs in meta-analysis and systematic reviews

Review	AE incidence		Withdrawals	
	Overall	GI-related	Any AE	GI-related
Celecoxib vs. NSAIDs for OA/RA				
<i>Pfizer-funded meta-analyses</i>				
<i>Deeks 2002⁶⁵</i>	-	-	RR 0.86 (0.72, 1.04)	RR 0.54 (0.42, 0.71)
<i>Moore 2005⁶⁶</i>	0.96 (0.94, 0.98)	0.84 (0.81, 0.87)	RR 0.86 (0.81, 0.91)	RR 0.75 (0.7, 0.8)
Celecoxib vs. individual NSAIDs for RA				
<i>Garner 2005a²⁰⁸ (Cochrane Collaboration Systematic Review)</i>				
<i>Celecoxib vs. Naproxen</i>				
	-	-	No differences (RR Range: 1.02-1.36)	No differences (RR Range: 0.26-0.61)
<i>Celecoxib vs. Diclofenac</i>				
	0.75 (0.62, 0.90)	0.95 (0.85, 1.04)	0.54 (0.36, 0.79)	0.36 (0.21, 0.60)
Rofecoxib vs. NSAIDs for OA				
<i>Watson 2000²⁰⁹ (Merck-funded meta-analysis)</i>				
6-month	-	0.86 (0.78, 0.95)	-	0.68 (0.50, 0.92)
12-month	-	0.88 (0.80, 0.97)	-	0.70 (0.52, 0.94)
<i>Garner 2005c⁸² (Cochrane Collaboration Systematic Review)</i>				
<i>Rofecoxib vs. Diclofenac</i>				
	No differences (RR range: 0.98-1.01)	-	12.5 mg: 0.71 (0.52, 0.97) 25 mg: 0.70 (0.51, 0.95)	-
<i>Rofecoxib vs. Ibuprofen</i>				
	NS (RR range: 0.98-1.04)	-	↓ risk in 2 of 3 RCTs	No differences in 3 of 4 RCTs
<i>Rofecoxib vs. Naproxen</i>				

No differences	0.55 (0.42, 0.73)	No differences	↓ risk in 2 of 3 RCTs
<i>Rofecoxib vs. Nabumetone</i>			
NR	NR	No differences	No differences
Rofecoxib vs. Naproxen in RA			
<i>Garner 2005b⁸³ (Cochrane Collaboration Systematic Review)</i>			
-	-	1.02 (0.92, 1.12)	0.74 (0.64, 0.85)

Tolerability profile of valdecoxib relative to NSAIDs appeared time-dependent as reported by a Pfizer-funded meta-analysis based on trials Pfizer provided.²¹⁰ Significant increases in overall adverse event incidence (RR 1.1; 95% CI 1.04, 1.2) and incidence of GI adverse events (RR 1.4; 95% CI 1.2, 1.6) for valdecoxib relative to NSAIDs did not lead to increased risk of discontinuation in RCTs of 6-12 weeks' duration. By 12-26 weeks, however, valdecoxib was associated with a more favorable tolerability profile than NSAIDs as reflected by significantly lower rates of overall adverse event incidence (RR 0.9; 95% CI 0.85, 0.93) and GI-related adverse events (RR 0.7; 95% CI 0.7, 0.8), which led to lower rates of discontinuation due to overall adverse events (RR 0.9; 95% CI 0.85, 0.93) and due to GI-related adverse events (RR 1.4; 95% CI 1.2, 1.6) for valdecoxib relative to NSAIDs.

COX-2 vs. COX-2.

Incidence of and withdrawals due to overall and GI-related adverse events were similar for celecoxib and rofecoxib across a manufacturer-funded meta-analysis⁶⁶ and a good-quality Cochrane review.⁸² The manufacturer-funded meta-analysis reported that rofecoxib and celecoxib were associated with similar risks of any adverse event (RR 0.97; 95% CI 0.84, 1.1), any GI-related adverse event (RR 0.87, 95% CI 0.74, 1.03), and GI-adverse event discontinuation (RR 0.7; 95% CI 0.5, 1.2) using data from five 6- to 12-week RCTs of patients with either OA or RA.⁶⁶ The Cochrane review of rofecoxib for osteoarthritis⁸² found no differences for either the total number of withdrawals (RR 0.93, 95% CI 0.76 to 1.14) or the number of withdrawals due to adverse events (RR 1.03, 95% CI 0.77 to 1.39) in five trials that compared celecoxib to rofecoxib.

Acetaminophen

We identified four systematic reviews that evaluated the efficacy and safety of acetaminophen compared with NSAIDs (selective or non-selective) for osteoarthritis.²¹¹⁻²¹⁴ The studies generally met all criteria for good-quality systematic reviews, except that three²¹²⁻²¹⁴ did not provide sufficient detail about trials that were excluded. The overall conclusion from the reviews was that NSAIDs are modestly superior to acetaminophen for general or rest pain (Table 18). For pain on motion and overall assessment of clinical response, NSAIDs also appeared modestly superior, though the differences were not always statistically significant.^{212, 213} Only two reviews assessed functional disability; neither found clear differences.^{212, 213}

Table 18. Pain relief in systematic reviews of acetaminophen versus NSAID

Systematic review	Date of last search	Number of head-to-head trials included	Main results for outcome of general or rest pain
Towheed, 2005 ²¹²	Through 8/02	5 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (SMD 0.32, 95% CI 0.08 to 0.56) and HAQ pain (SMD 0.27, 95% CI 0.05 to 0.48)

Zhang, 2004 ²¹⁴	Through 7/03	8 (3 trials evaluated coxibs)	NSAIDs superior using WOMAC scale (pooled ES 0.3, 95% CI 0.17 to 0.44) and clinical response rate (RR 1.24, 95% CI 1.08 to 1.41)
Lee, 2004 ²¹¹	Through 2/03	6 (1 trial evaluated a coxib)	NSAIDs superior for rest pain (weighted mean difference -6.33, 95% CI -9.24 to -3.41)
Wegman, 2004 ²¹³	Through 12/01	3 (no trials evaluated coxibs)	NSAIDs superior for general/rest pain (standardized mean difference 0.33, 95% CI 0.15 to 0.51)

The risk of adverse events with acetaminophen versus NSAIDs was assessed in three systematic reviews (Table 19).^{211, 212, 214} In two reviews, there were no differences in withdrawal due to any adverse event.^{212, 214} However, acetaminophen was associated with fewer gastrointestinal side effects compared with non-selective NSAIDs (though not compared with coxibs)^{212, 214} and fewer withdrawals due to gastrointestinal adverse events.²¹²

Table 19. Adverse events in systematic reviews of acetaminophen versus NSAID

Systematic review	Withdrawal due to adverse events	GI adverse events
Towheed, 2005 ²¹²	No difference (8% vs. 9%)	Withdrawal due to GI adverse event Naproxen or ibuprofen vs. acetaminophen: RR 2.15 (95% CI 1.05 to 4.42) Any GI adverse event Non-selective NSAID vs. acetaminophen: RR 2.24 (95% CI 1.23 to 4.08) Coxib vs. acetaminophen: RR 0.96 (95% CI 0.57 to 1.61)
Zhang, 2004 ²¹⁴	Not reported	GI discomfort Non-selective NSAID vs. acetaminophen: RR 1.39 (95% CI 1.07 to 1.80) Coxib vs. acetaminophen: RR 0.65 (95% CI 0.17 to 2.52)
Lee, 2004 ²¹¹	NSAID vs. acetaminophen: OR 1.45, 95% CI 0.93 to 2.27)	Not reported

Results of recent, good-quality randomized trials (not included in any of the systematic reviews) were consistent with the systematic reviews. One two-week trial (N=222) found that ibuprofen 1,200 mg/day was more effective than paracetamol 3,000 mg/day for pain relief (p<0.005) and functional disability using WOMAC scores (-20.8 versus -13.4, p<0.001).²¹⁵ Two cross-over trials of identical design (N=524 and 556) found that celecoxib was modestly superior to acetaminophen for WOMAC scores (difference in WOMAC score improvements ranged from 2.8 to 5.0 points on a 100-point scale), visual analogue pain scales (mean difference in scores ranged from 3.5 to 7.7 mm on a 100 mm scale), and patient preferences (53% and 50% favored celecoxib, versus 24% and 32% favored acetaminophen).²¹⁶ In all three trials, tolerability and safety were equivalent.

Clinical trials have not been large enough to assess serious but less common complications such as PUB, myocardial infarction, acute renal failure, or hypertension. However, observational studies provide some additional information about the safety of acetaminophen compared with NSAIDs. A good-quality nested case-control study of 1,197 cases and 10,000 controls from a population-based cohort of 458,840 persons in the General Practice Research Database found that current acetaminophen use was associated with a lower risk for symptomatic peptic ulcer (adjusted RR 1.9, 95% CI 1.5 to 2.3) than was NSAID use (adjusted RR 4.0, 95% CI

3.2 to 5.1) when each was compared with non-use.²¹⁷ There was no clear relationship between higher acetaminophen dose and increased risk for symptomatic ulcers. An earlier analysis on the same database also found that current acetaminophen use was associated with lower risk for upper gastrointestinal bleeds or perforations (adjusted RR 1.3, 95% CI 1.1 to 1.5) than was current NSAID use (adjusted OR 3.9, 95% CI 3.4 to 4.6), each compared with non-use.¹⁶⁸ A retrospective cohort study of elderly patients found that patients using lower doses of acetaminophen (<2,600 mg/day) had lower rates of GI events (defined as GI-related hospitalizations, ulcers, and dyspepsia) compared with users of NSAIDs (RR 0.73, 95% CI 0.67 to 0.80 for 1,951 to 2,600 mg/day), but the risks were similar at higher doses (RR 0.93 to 0.98).²¹⁸ Although GI hospitalization rates were not reported separately, the authors noted that dyspepsia was responsible for most of the increase in GI events in the high-dose acetaminophen groups. A meta-analysis on individual patient data from three earlier retrospective case-control studies (2472 cases) was consistent with the above studies.²¹⁹ It found that acetaminophen was associated with a minimal increase in the risk for serious upper gastrointestinal bleeding (OR 1.2, 95% CI 1.1 to 1.5). By contrast, non-selective NSAIDs were associated with higher risks, though estimates of risk varied considerably for different NSAIDs (OR 1.7 for ibuprofen to 34.9 for ketoprofen).

The association between renal failure and acetaminophen use has been evaluated in several case-control studies. Interpretation of these studies, however, is difficult because many had important flaws (such as failure to identify patients early enough in the course of their disease to insure that the disease had not led to a change in the use of analgesics, failure to specify diagnostic criteria, failure to adjust for the use of other analgesics, incompleteness of data on exposure, and use of proxy respondents) in the collection or analysis of data.²²⁰ The largest (926 cases) case-control study was designed to try to avoid many of these flaws.²²¹ It found that regular use of acetaminophen was associated with an increased risk for chronic renal failure (Cr >3.8 for men and >3.2 for women) compared with non-use (OR 2.5, 95% CI 1.7 to 3.6). Use of NSAIDs was not associated with an increased risk (OR 1.0). A prospective cohort study of 1,697 women in the Nurses' Health Study found that increased lifetime acetaminophen exposure was associated with a higher risk of decline in glomerula filtration rate of 30% or greater (p<0.001), though NSAIDs were not (p=0.88).²²² The absolute risk of renal function decline, however, appeared modest, even in women reporting high amounts of lifetime acetaminophen use. Compared with women consuming less than 100 g of cumulative acetaminophen, the odds of a decline in GFR of at least 30 mL/min per 1.73 m² for women consuming more than 3,000 g was 2.04 (95% CI, 1.28 to 3.24). By contrast, analyses of men in the Physicians' Health Study found no association between acetaminophen or NSAIDs and change in kidney function.^{223, 224} The risk of heart failure associated with acetaminophen has not been well-studied. In a single study using the General Practice Research Database, current use of acetaminophen was associated with a higher risk of newly diagnosed heart failure compared with non-use (RR 1.33, 95% CI 1.06 to 1.67), though the risk was lower compared with current use of NSAIDs (RR 1.59, 95% CI 1.23 to 2.05).¹⁹⁸

The risk of hypertension has been evaluated using data from the Nurses' Health Studies²²⁵⁻²²⁷ and the Physicians' Health Study.²²⁸ In the Nurses' Health Studies, acetaminophen and NSAIDs were associated with similar increases in risk of incident hypertension (Table 20). In the Physicians' Health Study, on the other hand, there was no association between NSAID or acetaminophen use and hypertension.

Table 20. Incidence of hypertension in the Nurses' Health Study and Physicians' Health Study according to

2223 **use of acetaminophen or NSAIDs**

Study	Acetaminophen use versus non-use: odds ratio	NSAID use versus non-use: odds ratio
Nurses' Health Study I (women 51 to 77 years old) ²²⁵	1.93 (1.30 to 2.88)	1.78 (1.21 to 2.61)
Nurses' Health Study II (women 34 to 53 years old) ²²⁵	1.99 (1.39 to 2.85)	1.60 (1.10 to 2.32)
Physicians' Health Study ²²⁸	1.08 (95% CI 0.87 to 1.34)	1.05 (95% CI 0.89 to 1.24)

2224 Although overdoses with acetaminophen can lead to potentially life-threatening
 2225 hepatotoxicity, it is not clear if hepatotoxicity is associated with therapeutic doses.¹⁵ We
 2226 identified no studies comparing the incidence of hepatotoxicity with therapeutic doses of
 2227 acetaminophen and NSAIDs. We also identified no studies comparing the incidence of
 2228 myocardial infarctions in persons using acetaminophen compared with NSAIDs.
 2229

2231 **Glucosamine and chondroitin**

2232 Data regarding the comparative efficacy of glucosamine versus NSAIDs in patients with
 2233 osteoarthritis are mixed. The most promising results have been observed in trials sponsored by
 2234 Rotta Research Laboratories, which manufacturers pharmaceutical grade glucosamine not
 2235 available in the U.S. Because the content and purity of over-the-counter glucosamine
 2236 preparations vary substantially, the results of the Rotta trials may not be directly applicable in the
 2237 U.S.²²⁹

2238 A recently updated (searches through November 2004), good-quality Cochrane review
 2239 included four short-term (4 to 8 weeks) head-to-head trials of glucosamine versus an oral NSAID
 2240 (ibuprofen or piroxicam).²³⁰ Two of the trials were rated 5 out of 5 on the Jadad scale, and the
 2241 other two were rated 3 or 4 out of 5. The Rotta Research Laboratories sponsored three of the
 2242 trials; the fourth²³¹ was also conducted in Europe, but funding information was not reported.
 2243 One of the trials has only been published as an abstract,²³² and analyses were based on data from
 2244 an unpublished manuscript. Two of the four trials found that glucosamine was superior to oral
 2245 NSAIDs for efficacy,^{231, 232} and two found no difference.^{233, 234} In pooled analyses, glucosamine
 2246 was superior to an oral NSAID for improving pain (three trials, SMD -0.40, 95% CI -0.60 to -
 2247 0.19), but not for improving function using the Lequesne Index (two trials, SMD -0.36, 95% CI
 2248 -1.07 to 0.35). Glucosamine was also associated with fewer adverse events (RR 0.29, 95% CI
 2249 0.19 to 0.44) and withdrawals due to toxicity (RR 0.06, 95% CI 0.01 to 0.25). Two small (N=40
 2250 and N=45), 12-week Canadian trials, neither funded by Rotta Research Laboratories, have also
 2251 recently been published. Neither found differences between glucosamine and ibuprofen for
 2252 general osteoarthritis pain²³⁵ or for temporomandibular joint osteoarthritis.²³⁶ Only limited details
 2253 of the study design were reported for the first trial, though the second met all criteria for a good-
 2254 quality study.
 2255

2256 Evidence regarding the efficacy of glucosamine compared with placebo has also been mixed.
 2257 The Cochrane review found that glucosamine was no better than placebo when the analysis was
 2258 restricted to the eight trials with adequate allocation concealment.²³⁰ By contrast, when all
 2259 placebo-controlled trials were included in the analysis, glucosamine was superior for both pain
 2260 and function using the Lequesne index. The benefits of glucosamine also varied substantially
 2261 depending on the preparation being studied. Specifically, glucosamine performed better in the

seven trials evaluating the Rotta preparation (a prescription formulation available in Europe) (SMD -1.31 , 95% CI -1.99 to -0.64) compared with the eight trials using non-Rotta preparations (SMD -0.15 , 95% CI -0.35 to 0.05). In fact, all of the five trials that found no benefit from glucosamine evaluated a non-Rotta brand of glucosamine and also had limited or no affiliation with a manufacturer of glucosamine. Older systematic reviews found that glucosamine was superior to placebo, but did not include several newer and higher quality trials that demonstrated no effect, and also noted important methodological flaws that could have exaggerated estimates of effect.^{237, 238} In all of the systematic reviews, rates of adverse events were no different between glucosamine and placebo.

We identified no trials comparing chondroitin sulfate to oral NSAIDs. Three systematic reviews evaluated the efficacy and safety of chondroitin compared with placebo. The most recent, fair-quality systematic review found indistinguishable efficacy for glucosamine and chondroitin and combined the results of the trials.²³⁸ When all trials were pooled, active treatment was associated with an increased likelihood of being a responder (RR 1.59 , 95% CI 1.39 to 1.83) compared with placebo. The results of the chondroitin trials were not reported separately. The chondroitin trials also received lower quality ratings than the glucosamine trials, but the effects of quality scores on the findings were not evaluated. Assessment of the effects of quality on assessments of estimates of benefit are important because an earlier, good-quality systematic review found that pooled effect sizes for pain relief were substantially lower for chondroitin trials with quality scores below the median (effect size 1.7 , 95% CI 0.7 to 2.7) compared with trials with quality scores above the median (ES 0.8 , 95% CI 0.6 to 1.0).²³⁷ Smaller chondroitin trials also reported higher effects. The third systematic review was also rated fair quality because it did not evaluate the effects of study quality on results.²³⁹ It found that chondroitin was superior to placebo for pain and function, but longer and larger studies were needed. All three systematic reviews found that chondroitin was tolerated as well as placebo, with only mild adverse events.

Results of a large (N=1,583), NIH-funded, randomized trial (Glucosamine/chondroitin Arthritis Intervention Trial) comparing placebo, celecoxib, glucosamine, chondroitin, and glucosamine plus chondroitin have been published in abstract form.²⁴⁰ Using pharmaceutical grade glucosamine hydrochloride (rather than the glucosamine sulfate commonly available in U.S. over the counter preparations) and chondroitin under an investigational new drug application, the study randomized patients stratified by baseline pain severity. It found that glucosamine plus chondroitin was superior to placebo for achieving a clinical response ($>20\%$ improvement in WOMAC Pain score), but only in the subgroup of patients with moderate to severe (WOMAC 301 to 400 mm) baseline pain (79% vs. 54.3%, $p=0.002$). There were no statistically significant differences between celecoxib and any of the other active treatment arms (glucosamine alone, chondroitin alone, or glucosamine plus chondroitin). The authors postulated that lack of effect in the mild baseline pain group could have been due in part to floor effects. High placebo response rates were also observed. All of the interventions were well tolerated.

Table 21. Response rates in the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)²⁴⁰

Intervention	All patients	Moderate-severe baseline pain (WOMAC pain score 301-400 mm)	Mild baseline pain (WOMAC pain score 125-300)
Placebo	60.1%	54.3%	61.7%
Celecoxib	70.1% ($p=0.08$ vs. placebo)	69.4% ($p=0.06$ versus placebo)	70.3% ($p=0.04$ vs. placebo)
Glucosamine	64.0%	65.7%	63.6%

Chondroitin	65.4%	61.4%	66.5%
Glucosamine + chondroitin	66.6% (p=0.09 vs. placebo)	79.2% (p=0.002 vs. placebo)	62.9%

Key Question 1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?

Duration and dose appear to have important effects on benefits and harms associated with selective and non-selective NSAIDs, though some data are conflicting. Results of the VIGOR trial indicate that the risk of cardiovascular events rose sharply only after 8 months of treatment with rofecoxib.¹¹² Several meta-analyses sponsored by the manufacturer of rofecoxib found no association between rofecoxib use and cardiovascular risk, but most of the included trials evaluated lower doses of rofecoxib than did VIGOR, and followed patients for less than 8 months.^{123, 124} On the other hand, a recent independent meta-analysis of rofecoxib trials found that the increased risk of cardiovascular events associated with rofecoxib did not vary depending on the dose or duration of treatment.¹²⁵

Limited observational study evidence also suggests that risk of CV events associated with rofecoxib does not vary significantly depending on dose¹⁴⁰ or duration.¹⁴⁷ Odds of acute MI were greater overall for rofecoxib relative to celecoxib in a case-control study of low-income Medicare beneficiaries (mean age 79 years) exposed to treatment for ≤ 90 days.¹⁴⁰ The risk estimate for those taking rofecoxib > 25 mg (OR 1.70; 95% CI 1.07, 2.71) was greater than for those taking ≤ 25 mg (OR 1.21; 95% CI 1.01, 1.44), however.¹⁴⁰ Risk of CV events was similar for rofecoxib and meloxicam, regardless of duration, in a cohort study in which data was ascertained from an England National Health Services database using a Prescription Event Monitoring system.²⁴¹

Analysis of the CLASS data suggests that celecoxib was more effective at 6 months compared with longer duration of exposure. In fact, the GI safety benefits seen at 6 months were no longer apparent after 12 months.¹⁰³ Duration of treatment could also influence the cardiovascular safety of celecoxib. Celecoxib was not associated with excess cardiovascular risk when compared with diclofenac or ibuprofen in the CLASS trials⁵⁷ or in meta-analyses^{111, 122} of trials of patients with arthritis. However, results of the APC polyp prevention trial¹²⁹ suggests that the lack of an association could be due in part to the short-term nature of most of the osteoarthritis trials. At 33 months, the APC trial was significantly longer than the arthritis treatment trials, and was also the first to clearly show an increased risk of cardiovascular events associated with celecoxib. It also found that the risk of cardiovascular events increased with higher doses of celecoxib.

The risk for GI bleeding with non-selective NSAIDs also appears to increase with higher doses.^{176, 219} By contrast, the risk of bleeding associated with acetaminophen was not associated with dose in one meta-analysis of three case-control studies,²¹⁹ though there was a modest dose response in another case-control study of elderly patients.²¹⁸ At low over-the-counter doses, the risk of GI hospitalizations associated with aspirin, acetaminophen, and ibuprofen were similar to background rates in patients with rheumatoid arthritis or osteoarthritis in the ARAMIS database.²⁴² We found no studies evaluating the effects of dose of non-selective NSAIDs on

cardiovascular risk. We also found no studies evaluating the effects of alternative drug strategies such as intermittent dosing or drug holidays on risks and benefits of oral medication use.

Key Question 2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?

Demographic subgroups include age, sex, and race.

In general, the risk of cardiovascular, cardiorenal, and gastrointestinal adverse events associated with NSAIDs increase with age.¹² In one UK population, for example, the risk of adverse gastrointestinal outcomes in patients taking selective or non-selective NSAIDs was 1.36 per 1,000 patient-years for all patients 25 years or older, but 4.03 per 1,000 patient-years in patients aged 65 or more.¹³⁴ Similarly, the risk of myocardial infarction was 1.71 per 100 person-years for all patients 25 years or older, but 4.57 per 100 person-years for those 65 or older.¹⁴¹ We found no study designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary with age. However, even if the relative benefits and harms associated with different drugs are consistent across age groups, the absolute effects would increase substantially with age because of the differences in baseline risk.

Studies that have evaluated the efficacy and safety of selective and non-selective NSAIDs in average-risk elderly patients have generally reported similar findings compared with studies in populations with younger adults. An original data meta-analysis of three celecoxib trials, for example, found that celecoxib 200 mg/day or 400 mg/day and naproxen 1,000 mg/day were similar in elderly patients when evaluating WOMAC and SF-36 scores.²⁴³ For the SF-36, there were no statistically significant differences: naproxen scored better than celecoxib 200 mg on four of 10 components of the SF-36, while celecoxib 200 mg scored better on six, including general health. Celecoxib 200 mg was significantly better than placebo on nine of the 10 components, while naproxen was significantly better than placebo on seven. The study also confirmed that the overall incidence of GI adverse events was lower with celecoxib; the difference was about one event in 20 patients for celecoxib 200 mg and one in 10 for celecoxib 400 mg.

Data suggesting differential effects of oral medications for osteoarthritis according to gender, ethnicity, or race are scant. In most of the published trials, a majority of subjects were women. As noted in the discussion of acetaminophen, results from the Nurses' Health Studies suggest that acetaminophen is associated with modest reductions in renal function in women,²²⁵ but results from the Physicians' Health Study have found no association between acetaminophen use and renal dysfunction in men.²²⁸ The effects of different NSAIDs in specific ethnic minorities have only been evaluated in small studies. In a randomized crossover study of 25 black and Hispanic patients on ACE inhibitors, peak increases in blood pressure were similar in patients on diclofenac compared with celecoxib.²⁴⁴ An observational study of 120 Native American patients switched to rofecoxib found that the mean systolic blood pressure increased by 2.9 mm Hg overall ($p=0.015$) and by 4.8 mm Hg ($p=0.009$) in hypertensive patients.²⁴⁵ We did not find any other publications focusing on the differential efficacy or safety of coxibs in African-Americans, Hispanics, or other ethnic minorities.

Co-existing diseases include history of previous bleeding due to NSAIDs; peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure.

Rates of recurrent ulcer bleeding were similar for celecoxib 200 mg and the combinations of extended-release diclofenac 75 mg BID plus omeprazole 20 mg QD²⁴⁶ or naproxen 250 mg TID plus lansoprazole 30 mg QD²⁴⁷ in two fair-quality, 24-week, parallel trials involving a total of 529 patients who presented with a bleeding ulcer (Table 22). There were also no differences between celecoxib and either combination therapy in other adverse events including GI, renal, and cardiovascular symptoms or in rates of withdrawals due to adverse events. One exception was that celecoxib 200 mg QD was associated with a higher rate of dyspepsia than naproxen 250 mg TID plus lansoprazole 30 mg QD.²⁴⁷ The high rates of recurrent bleeding in both the celecoxib-treated patients and in the combination therapy groups—over 10 times as high as the rate in the CLASS trial—suggest that NSAIDs and coxibs should be used with caution, if at all, in patients who have a recent history of a bleeding ulcer.

Table 22. Celecoxib in patients with bleeding ulcer history

Study Sample Size	Treatments	Recurrent ulcer bleeding at 6 months (difference; 95% CI)	Other adverse events	Withdrawals due to adverse events
Chan 2002 ²⁴⁶ n=287	Celecoxib 200 mg BID Diclofenac 75 mg BID plus omeprazole 20 mg QD	4.9% vs. 6.3% (-1.5%, CI -6.8, 3.8%; NS)	No differences	13.3% vs. 11.9%, NS*
Lai 2005 ²⁴⁷ ** n=242	Celecoxib 200 mg QD Naproxen 250 mg TID plus lansoprazole 30 mg QD	3.7% vs. 6.3% (-2.6; CI -9.1, 3.7; NS)	No differences for all but dyspepsia: 15% vs. 5.7%, p=0.02	10% vs. 7.4%, NS

*Includes withdrawals due to lack of efficacy

**Open trial

We found no randomized controlled trial evaluating the risk of bleeding with rofecoxib compared with celecoxib in high-risk patients. A Danish population-based case-control study of high-risk patients with previous gastrointestinal diseases found that the risk of upper gastrointestinal bleeding was associated with rofecoxib (OR 2.1, 95% CI 1.2 to 3.5) and non-selective NSAIDs (OR 3.3, 95% CI 2.4 to 4.4), but not with celecoxib (OR 1.3, 95% CI 0.7 to 2.8).¹⁰

We found no study designed to assess whether the relative harms and benefits associated with different oral treatments for osteoarthritis vary according to underlying cardiovascular or renal risk. If the relative risk of cardiovascular harms is consistent across risk groups for a particular drug, the absolute effects would be expected to be substantially greater in patients at higher baseline risk compared with patients at average risk.

Only a few trials have evaluated the effects of different oral medications on cardiovascular and cardiorenal events specifically in high-risk patients. Three randomized trials sponsored by the manufacturer of celecoxib found higher rates of hypertension or blood pressure increases in patients randomized to rofecoxib compared with patients randomized to celecoxib, but no differences in discontinuations due to adverse events or for episodes of heart failure.^{89, 94, 193} As noted earlier, the results of these trials must be interpreted cautiously because they evaluated non-equivalent doses of rofecoxib and celecoxib, and because one of the trials⁸⁹ had important baseline differences suggesting inadequate randomization.

A meta-analysis funded by the manufacturer of rofecoxib found that in a high-risk subgroup of patients in whom aspirin was indicated (history of cardiovascular disease), rofecoxib was not

associated with an increased risk of myocardial infarction compared with either placebo or non-selective NSAIDs.¹²⁴ However, the duration of the included trials may have been too short (median 3½ months) to detect an increased risk, and only a minority of patients received the high dose of rofecoxib evaluated in the VIGOR trial.

We found no trials evaluating comparative risks of different oral medications in patients with known congestive heart failure. A recent, good-quality population based retrospective cohort study, however, found that the risk of death and recurrent congestive heart failure was higher in patients prescribed NSAIDs (HR 1.26, 95% CI 1.00 to 1.57) or rofecoxib (HR 1.27, 95% CI 1.09 to 1.49), each compared with those prescribed celecoxib.¹⁹⁷ We also found no trials comparing the risks and benefits of different oral medications in patients with known renal failure.

Concomitant anticoagulant or aspirin use.

Concomitant anticoagulants. Concomitant use of anticoagulants and non-selective NSAIDs increases the risk of GI bleeding three- to six-fold compared to anticoagulants alone.^{248, 249} Several observational studies have evaluated whether COX-2 selective agents are associated with a lower risk for bleeding compared with non-selective agents in patients on anticoagulation.

A good-quality nested case-control study of elderly (>66 years old) patients on warfarin in Ontario, Canada, evaluated the association between hospitalization for upper gastrointestinal bleeding (361 cases) and use of selective or non-selective NSAIDs.²⁵⁰ It found that after adjustment for potential confounders (antiplatelet agents, hypoglycemic agents, glucocorticoids, gastroprotective agents, history of previous bleed, and comorbidities), recent use of non-selective NSAIDs (OR 1.9, 95% CI 1.4 to 3.7), celecoxib (1.7, 95% CI 1.2 to 3.6), and rofecoxib (2.4, 95% CI 1.7 to 3.6) were all associated with increased and overlapping risks for upper gastrointestinal bleeding, compared with non-use. Because this study relied on pharmaceutical databases to identify exposures prior to hospitalization, it could not assess the confounding effects of over-the-counter use of aspirin, other NSAIDs, or acid suppressive medications. It also was unable to control for variations in INR level and the risk for bleeding.

A smaller, fair-quality nested case-control study of patients in the Netherlands evaluated the risk of bleeding in anticoagulated patients receiving partially selective (meloxicam or nabumetone) COX-2 inhibitors or non-selective NSAIDs.²⁵¹ No case (N=154) received either celecoxib or rofecoxib. This study also differed from the Ontario study in that it included all cases of minor visible bleeding, hematoma, or black tarry stools. It used a questionnaire to assess exposure status and comorbidities. Patients were interviewed over the phone if answers were incomplete or unclear. The response rates were significantly higher in the cases (approximately 70%) compared with controls (approximately 31%). The study found that non-selective NSAIDs were associated with an increased risk of bleeding compared with partially selective NSAIDs after adjustment for duration of use and INR level (OR 3.07, 95% CI 1.18 to 8.03).

A July 2003 publication reported results from an open, crossover trial of celecoxib 200 mg and rofecoxib 25 mg in 18 patients with OA, RA, or chronic pain who were stable (three consecutive INRs within 15% of each other) on warfarin therapy.²⁵² The trial was designed to measure mean change in INR and safety parameters. Similar rates of edema, heart failure and other adverse events were found for celecoxib and rofecoxib. The INR increased by 5% to 15% between weeks one and three for both coxibs. Four minor bleeds were reported, with none associated with a significant decrease in hemoglobin concentration.

We found no studies evaluating risks and benefits of concomitant anticoagulants and aspirin in patients with arthritis. Combination therapy has been studied in patients with indications for thromboembolic prophylaxis. However, the results of those studies are not directly applicable to patients with arthritis because of important differences in the populations (particularly with regard to cardiovascular risk), and because aspirin was used in lower, prophylactic doses (rather than anti-inflammatory and analgesic doses). One fair-quality meta-analysis (did not evaluate quality of included trials) found that major bleeding risk was increased with warfarin plus aspirin versus warfarin alone (at the same intensity) in patients with mechanical heart valves (3 trials, RR 1.58, 95% CI 1.02 to 2.44).²⁵³ In patients with recent myocardial infarction or atrial fibrillation (one trial each), the increase in risk was not statistically significant (RR 3.07, 95% CI 0.33 to 28.38 and RR 2.13, 95% CI 0.20 to 23.03, respectively). In patients with mechanical heart valves, the increase in bleeding risk was offset by a reduction in thromboembolic events (RR 0.33, 95% CI 0.19 to 0.58), and there was no difference in all-cause mortality (RR 0.78, 95% CI 0.29 to 1.83). Other evidence on the risks and benefits of combination therapy has focused on comparing warfarin plus aspirin to aspirin alone. A recent good-quality meta-analysis of 10 trials, for example, found that the combination of warfarin plus aspirin increased the risk of major bleeding compared with aspirin alone following myocardial infarction or the acute coronary syndrome (RR 2.5, 95% CI 1.7 to 3.7).²⁵⁴ However, the increase in bleeding risk was offset by lower risks for myocardial infarction, ischemic stroke, and revascularization. Mortality did not differ.

No study evaluated risk of bleeding in anticoagulated patients on acetaminophen compared with those on NSAIDs. A small, randomized controlled trial found that acetaminophen was associated with greater increases in INR levels compared with placebo.²⁵⁵ Several observational studies have also found an association between excess anticoagulation and use of acetaminophen.^{256, 257} However, changes in INR are not the only important factor for predicting increased risk of bleeding. NSAIDs, for example, also affect platelet function and disrupt the gastric mucosal lining. Studies evaluating actual bleeding complications are necessary to better assess the comparative risks from acetaminophen and other NSAIDs.

No studies evaluated risk of bleeding in anticoagulated patients on glucosamine, chondroitin, or topical agents.

Concomitant aspirin. Beneficial effects of COX-2 selective inhibition on GI complication rates appear to be attenuated or eliminated by the concomitant use of aspirin. In the 20 per cent of patients in the CLASS trial who took aspirin in addition to their study drug, there was no difference in ulcer complications or ulcer complications plus symptomatic ulcers in patients randomized to celecoxib versus those randomized to diclofenac, ibuprofen, or the two NSAID comparators combined.¹⁰² Similarly, a meta-analysis of randomized controlled trials found that the beneficial effects of celecoxib on risk of endoscopically detected ulcers were reduced in patients on prophylactic aspirin (RR 0.49, 95% CI 0.28 to 0.86) compared with those not on aspirin (RR 0.27, 95% CI 0.16 to 0.48).⁶⁵ This analysis excluded the results of the CLASS trials because they did not evaluate endoscopic ulcers as an outcome and because of high, differential withdrawal rates. A re-analysis that included the full CLASS trial results found no benefit (rather than a reduced benefit) from celecoxib in patients on aspirin (RR 0.96, 95% CI 0.63 to 1.46),²⁵⁸ but the appropriateness of combining data from trials reporting endoscopic ulcers with data from the CLASS trials on withdrawal rates, symptomatic ulcers, and ulcer complications, is disputed.²⁵⁹ Another meta-analysis found that use of aspirin increased the rate of endoscopic ulcers by about 6% in patients randomized to celecoxib (4.2% without aspirin and 9.9% with

aspirin) and in those randomized to a non-selective NSAID (17.6% and 23.8%).⁶⁶ A recent trial that randomized osteoarthritis patients to placebo, enteric-coated aspirin (81 mg/day), rofecoxib 25 mg/day + aspirin 81 mg/day, or ibuprofen 2,400 mg/day found that the rate of endoscopic ulcers in the rofecoxib + aspirin arm (16.1%) was similar to the rate in the ibuprofen alone arm (17.1%); both rates were significantly higher than the placebo (5.8%) and aspirin alone (7.3%) arms.²⁶⁰ A meta-analysis of aspirin users in two trials comparing celecoxib 200 mg daily and rofecoxib 25 mg daily found that celecoxib was associated with a lower rate of withdrawals due to GI adverse events than rofecoxib (0.7% vs. 3.9%, $p < 0.05$), as well as with GI symptoms.²⁶¹ However, there were no reported serious GI events. Nonequivalent dosing of the COX-2 inhibitors, pooling of data across trials, and post-hoc subgroup analyses of the aspirin-users data limit interpretation of these results.

The effects of aspirin use on cardiovascular risks associated with COX-2 inhibitors and non-selective NSAIDs have not been well studied. In particular, randomized trials data are lacking. The VIGOR trial, for example, did not allow patients to take aspirin. In a polyp prevention trial of rofecoxib, use or non-use of low-dose aspirin did not affect the observed increased risk of thrombotic events.¹⁹² Consistent with that finding, two large observational studies on the UK GPRD¹⁶⁹ and QRESEARCH¹⁴¹ databases found no significant interaction between concurrent NSAID and aspirin use and the risk of myocardial infarction. On the other hand, other observational studies suggest that NSAIDs interfere with the cardioprotective effects of aspirin. One case-control study, for example, found that non-selective NSAID use reduced the risk of myocardial infarction only in patients who were not already on aspirin.¹⁷⁸ Another observational study found that in patients with known cardiovascular disease, there was a higher rate of overall mortality (adjusted hazard ratio 1.93, 95% CI 1.30 to 2.87) and cardiovascular death among users of ibuprofen plus aspirin compared with aspirin use alone, suggesting that ibuprofen (or other NSAIDs) could interfere with the cardioprotective effects of aspirin.²⁶² However, this study only evaluated small numbers of patients on NSAIDs, and did not adjust for important comorbidities.

Key Question 3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or proton pump inhibitors?

Misoprostol, standard- and double-dose H2 blockers and PPIs were all effective in reducing the risk of NSAID-associated endoscopic gastric and duodenal ulcers relative to placebo in three good-quality systematic reviews²⁶³⁻²⁶⁵ of numerous randomized controlled trials of OA/RA patients.^{8, 46, 75, 263, 266-292} H2 blockers,²⁹¹⁻³⁰¹ misoprostol (RR 0.36, 95% CI 0.20 to 0.67), and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers, but not serious cardiovascular or renal illness or death.²⁶⁵

Misoprostol has been studied most extensively and is the only agent proven to decrease risk of ulcer complications (MUCOSA).²⁸⁸ In a large, good-quality trial, misoprostol was associated with a rate of definite ulcer complications of 25/4404 (0.6%) compared to 44/4439 (0.9%) with placebo ($p = 0.049$).²⁸⁸ However, misoprostol is also the only agent to be associated with a significant risk of treatment withdrawal due to nausea (RR=1.30, 95% CI 1.08 to 1.55), diarrhea (RR=2.40, 95% CI: 2.05 to 2.81), and abdominal pain (RR=1.36, 95% CI 1.20 to 1.55).

Table 23. Placebo-controlled trials of gastroprotective agents²⁶³⁻²⁶⁵

Treatment	# PCT studies Duration	Prevention of endoscopic ulcers		Prevention of clinical GI events*
		Gastric	Duodenal	
Misoprostol	1-1.5 months: 8 ≥ 3 months: 11	1-1.5 months: RR=0.17, 95% CI: 0.09 to 0.31 3 months: RR=0.26; 95% CI 0.17 to 0.39	1-1.5 months: RR=0.28; 95% CI 0.09-0.31 3 months: RR=0.47, 95% CI 0.33 to 0.69	Silverstein 1995 (MUCOSA): OR 0.598; 95% CI 0.364 to 0.982
H2 blockers	Standard doses (150 mg): 7 Double doses (300 mg): 3 1-3 months	Standard dose: insignificant effect Double dose: RR=0.44, 95% CI: 0.026 to 0.74	Standard dose at 1 and 3 months: RR=0.24, 95% CI: 0.10 to 0.57 and RR=0.36, 95% CI: 0.18 to 0.74 Double dose: 0.26, 95% CI 0.11 to 0.65	None
PPIs	4 Duration NR	RR=0.40, 95% CI 0.32 to 0.51	RR 0.19, 95% CI 0.09 to 0.37	None

*Upper GI hemorrhage, perforation, pyloric obstruction, death)

Table 24 reflects the results from five trials^{46, 278, 285, 290, 292} that directly compare one gastroprotective agent with another, as reported in the CCOHTA review.²⁶⁴ Both misoprostol and omeprazole are superior to ranitidine for the prevention of gastric ulcers. Omeprazole and lansoprazole appear to be superior to misoprostol and ranitidine for the prevention of duodenal ulcers.

Table 24. Head-to-head trials of gastroprotective agents²⁶⁴

Comparison	Gastric	Reductions in ulcer risk
		Duodenal
Misoprostol vs. ranitidine* (2 trials; n=600)	RR=0.12 95% CI 0.03 to 0.89	No differences
Omeprazole 20 mg vs. ranitidine 150 mg (1 trial, n=425)	RR=0.32 95% CI 0.17 to 0.62	RR=0.11 95% CI 0.01 to 0.89
PPI** vs. misoprostol***	No differences	RR=0.29 95% CI 0.15 to 0.56

*standard dose

**omeprazole or lansoprazole

***secondary prophylaxis trials

Key Question 4. What are the benefits and safety of treating osteoarthritis with oral medications as compared with topical preparations?

Topical NSAIDs - Efficacy

Four trials directly compared topical and oral NSAIDs for osteoarthritis. Two recent good-quality systematic reviews^{302, 303} included three³⁰⁴⁻³⁰⁶ of these trials (an older systematic review was excluded because its results appear outdated.³⁰⁷). One systematic review (by Lin et al³⁰²) only included osteoarthritis trials, while the other systematic review (by Mason et al³⁰³) included osteoarthritis and other chronic pain conditions. The systematic reviews also used different methods for abstracting and pooling efficacy data. Specifically, the primary outcome in Mason

et al was a dichotomous outcome: the proportion of patients with clinical success (defined as approximately a 50% reduction in pain) at the end of the trial. By contrast, the primary outcome used by Lin et al was continuous: the difference in standardized effect sizes for the outcomes of pain, function, or stiffness measured at the end of each week of treatment. Two^{305, 306} of the trials received 5 out of 5 points on the Jadad quality scale; the third³⁰⁴ received a score of 3.³⁰³ Mason et al found that topical and oral NSAIDs were equivalent for clinical success after 3 to 4 weeks (pooled relative risk 1.1; 95% CI 0.9 to 1.3).³⁰³ Although Lin et al found that topical NSAIDs were inferior to oral NSAIDs for pain and function after one week of treatment, this finding was based on data from only one RCT (ES -0.38 for pain, 95% CI -0.66 to -0.10 and ES -0.32 for function, 95% CI -0.60 to -0.04).³⁰² There were no significant differences between topical and oral NSAIDs after 2 (one RCT), 3 (two RCTs) or 4 (one RCT) weeks. Effect sizes could not be calculated for one of the three RCTs.³⁰⁴

The largest and longest trial (by Tugwell et al) comparing topical and oral NSAIDs was published in 2004—too late to be included in the systematic reviews.³⁰⁸ This good-quality study found that the proportion of responders (as defined by Outcomes Measures in Arthritis Clinical Trials and the Osteoarthritis Research Society VI recommendations) at 12 weeks was similar in patients randomized to topical or oral diclofenac (66% vs. 70%, p=0.37). There were also no clinically relevant differences for the outcomes of mean change in pain scores, physical function, or patient global assessment.

We pooled rates of clinical response from the four trials (including Tugwell et al) comparing topical and oral NSAIDs, using intention-to-treat (missing values=failure) results and methods similar to the Mason meta-analysis. We found no differences between topical and oral NSAIDs (OR=0.95, 95% CI 0.70-1.30). It should be noted that the Sandelin study, which reported the lowest efficacy for topical versus oral NSAIDs, evaluated topical eltenac, a drug that is no longer being investigated for use in humans.³⁰⁵

Table 25. Head-to-head trials of topical versus oral NSAID for osteoarthritis

Author, year	Condition Number enrolled	Comparison	Duration of study	Definition of clinical success
Dickson, 1991 ³⁰⁴	OA of knee 235	Piroxicam 0.5% Ibuprofen 400 mg po tid	4 weeks	Patient global assessment 'good' or 'excellent'
Sandelin, 1997 ³⁰⁵	OA of knee 208	Eltenac 1% gel Diclofenac 50 mg bid	4 weeks	Physician global assessment 'good'
Zacher, 2001 ³⁰⁶	OA of fingers 321	Diclofenac 1% gel Ibuprofen 400 mg po tid	3 weeks	>=40% improvement in pain on 100 mm VAS
Tugwell, 2004 ³⁰⁸	OA of knee 622	Diclofenac 1.5% in carrier with 45.5% DMSO Diclofenac 50 mg po tid	12 weeks	OMERACT VI criteria ³⁶ for clinical responder

Figure 1. Clinical success in trials comparing a topical versus an oral NSAID

Only three small (sample sizes 40, 85, and 129), short-term (2- to 4-week) trials directly compared different topical NSAIDs for chronic pain conditions. They found no differences between topical diclofenac and indomethacin,³⁰⁹ topical flurbiprofen and piketoprofen,³¹⁰ or topical ketoprofen and diclofenac.³¹¹

The two systematic reviews came to somewhat different conclusions regarding the efficacy of topical NSAIDs compared with placebo. Lin et al found that topical NSAIDs were effective only during the first 2 weeks of treatment.³⁰² However, their conclusions at 3 and 4 weeks were entirely based on three trials that evaluated eltenac gel (no longer produced or studied for human use) or a topical salicylate (no longer classified as a topical NSAID). Mason et al, on the other hand, found NSAIDs superior to placebo (relative benefit 1.9, 95% CI 1.7 to 2.2) from 14 placebo-controlled trials of varying duration, with a number needed to treat for one case of clinical success (approximate 50% reduction in pain) of 4.6 (95% CI 3.8 to 5.9).³⁰³ Results were not sensitive to quality ratings, trial sample size, outcome measured, or condition (knee osteoarthritis versus other musculoskeletal conditions).

Four placebo-controlled trials of topical NSAIDs for osteoarthritis³¹²⁻³¹⁵ have been published since the systematic reviews were conducted. Three of these trials lasted longer than 4 weeks, and all found topical NSAIDs effective. The results of these trials are summarized in Table 26 for the dichotomous outcome “clinical success.” The longest trial of topical versus oral NSAIDs—a 2-year study of topical versus oral ibuprofen funded by the UK Health Technology Assessment Program—will not be completed until 2007.³¹⁶

Table 26. Clinical success rates in recent placebo-controlled trials of topical NSAIDs

Study	Duration	Definition of ‘clinical success’	Treatment group	Proportion of subjects classified as ‘clinical success’ at end of study period
Bookman, 2004 ³¹³	4 weeks	>50% reduction in pain	Diclofenac Vehicle-control Placebo	44/84 (52.4%) 26/79 (32.9%) 28/84 (33.3%)
Roth, 2004 ³¹⁴	12 weeks	>50% reduction in pain	Diclofenac Vehicle-control	79/163 (48.5%) 55/159 (34.6%)
Baer, 2005 ³¹²	6 weeks	>50% reduction in pain	Diclofenac Vehicle-control	46/105 (43.8%) 27/107 (25.2%)
Trnavsky, 2004 ³¹⁵	7 days	Reduction of >18 mm in VAS or >23% from baseline for pain	Ibuprofen Placebo	21/25 (84.0%) 10/25 (40.0%)

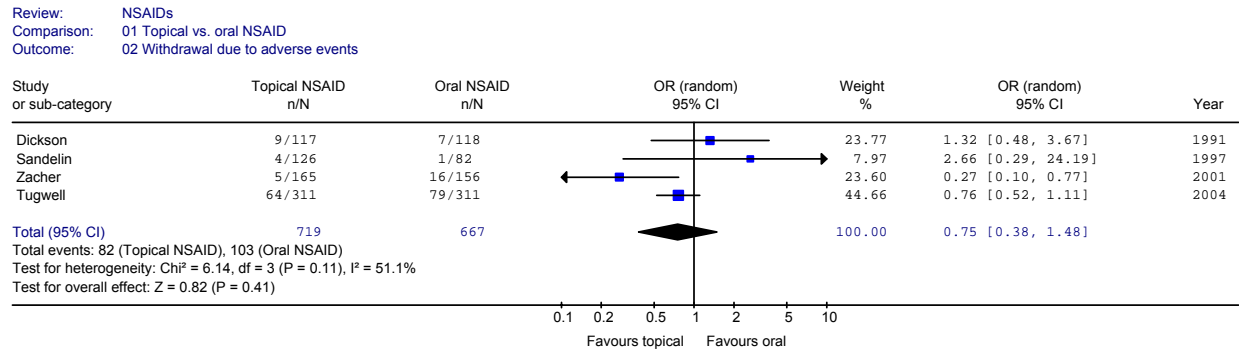
Placebo-controlled trials also suggest that topical NSAIDs differ with regard to efficacy. Topical diclofenac, which has been evaluated in the most (eight) trials, was consistently superior to placebo or associated with a trend towards superiority.^{303, 312-314} Several of these trials

evaluated a proprietary compound of topical diclofenac in a carrier containing DMSO (Pennsaid®). Ibuprofen was superior to placebo for chronic pain conditions in three RCTs.^{303, 315} By contrast, evidence regarding the efficacy of other topical NSAIDs for chronic conditions is much more scant (see Mason,³⁰³ Additional Files 4 and 5). Four trials found that topical piroxicam was no better than placebo, homeopathic gel, or glyceryl trinitrate 1% cream. One RCT found topical ketoprofen no better than placebo. Topical felbinac, flufenamate, and indomethacin have only been evaluated in one or two small trials each. Evidence on topical flurbiprofen was mixed: one trial found topical flurbiprofen superior to placebo, but another found no differences.

Topical NSAIDs - Safety

Topical NSAIDs were associated with increased local adverse events (skin reactions such as rash, itch, and burning) compared with oral NSAIDs in two recent systematic reviews.^{302, 303} However, there were no differences for total adverse events, systemic adverse events, withdrawal due to adverse events, gastrointestinal events, or central nervous system events. For the outcome of withdrawal due to adverse events, we found no differences when we pooled the three trials included in the earlier reviews and a fourth,³⁰⁸ more recent trial.

Figure 2. Withdrawal due to adverse events in trials comparing a topical to an oral NSAID



Among the head-to-head trials, Tugwell et al provides the most information about adverse events because it has the largest sample size, the longest duration of follow-up, and used pre-specified definitions for adverse events and adverse-event severity.³⁰⁸ Topical diclofenac was associated with more local skin reactions but with fewer systemic and laboratory adverse events (Table 27).

Table 27. Adverse events from a trial³⁰⁸ comparing topical to oral diclofenac

Adverse event	Topical diclofenac in DMSO carrier (n=311)	Oral diclofenac (n=311)	P value for difference
Withdrawal due to adverse event	21%	25%	0.15
Increase in mean blood pressure >= 5 mm Hg	24%	28%	0.30
Dry skin	27%	1%	<0.0001
Rash	12%	2%	<0.0001
Pruritus	6%	0.6%	<0.0001
Gastrointestinal events (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, melena, nausea, vomiting)	35%	48%	0.0006

Severe gastrointestinal event (defined as producing significant impairment of functioning and definite hazard to patient's health)	2.6%	10.2%	0.0003
Melena	1%	2%	0.36
Asthma	3%	0.6%	0.02
Dizziness	0.6%	4%	0.002
Dyspnea	0%	2%	0.01
Hemoglobin went from normal to abnormal	2%	10%	<0.0001
Alanine transaminase increase to >3 times the upper limit or normal	1.1%	4.7%	0.01
Creatinine clearance went from normal to abnormal	4%	10%	0.01

No RCT was adequately designed to assess risks for serious but uncommon adverse events such as myocardial infarction, renal failure, or gastrointestinal bleeding. We identified one case-control study (1,103 cases) that evaluated the risk of hospital admission for upper gastrointestinal bleeding and perforation in patients taking topical NSAIDs.³¹⁷ After adjusting for the confounding effects of exposure to oral NSAIDs and ulcer healing drugs, there was no association between exposure to topical NSAIDs within 45 days of an upper GI bleed (OR 1.45, 95% CI 0.84 to 2.50 with community controls and OR 1.06, 95% CI 0.60 to 1.88 with hospital controls). By contrast, oral NSAIDs were associated with increased risk (OR 2.59, 95% CI 2.12 to 3.16 for community controls and 2.00, 95% CI 1.60 to 2.50 for hospital controls). In a nested case-control study of the General Practice Research Database, topical NSAID use was not associated with symptomatic peptic ulcer (RR=1.0 versus non-use, 95% CI 0.6 to 1.7), though oral NSAID use was associated with increased risk (RR=4.0, 95% CI 3.2 to 5.1).²¹⁷

We identified one case-control study of similar design that found that exposure to topical NSAIDs was not associated with acute renal failure (adjusted OR 1.33, 95% CI 0.79 to 2.24 using community controls and 1.04, 95% CI 0.60 to 1.83 using hospital controls).³¹⁸ Recent exposure to oral NSAIDs, on the other hand, was associated with increased risk of renal failure using either community (adjusted OR 2.20, 95% CI 1.49 to 3.25) or hospital (adjusted OR 1.84, 95% CI 1.15 to 2.93) controls. We identified no studies comparing the risk of cardiovascular events in persons on topical versus oral NSAIDs.

Topical salicylates (including capsaicin)

We identified no trials comparing topical salicylates to oral or topical NSAIDs. One recent good-quality systematic review found that topical salicylates were significantly better than placebo when data from six trials were pooled (relative benefit 1.5, 95% CI 1.3 to 1.9; NNT 5.3, 95% CI 3.6 to 10.2).³⁰ However, the three higher quality trials found no significant benefit (relative benefit 1.3, 95% CI 0.98 to 1.6). Local adverse events were rare, but the quality of adverse-event reporting was poor.

We identified no trials comparing topical capsaicin to oral or topical NSAIDs. One recent good-quality systematic review found that for chronic musculoskeletal pain, capsaicin was superior to placebo for achieving clinical success (defined as approximately a 50% reduction in pain), with a relative benefit of 1.5 (three trials, 95% CI 1.1 to 2.0) and number needed to treat of 8.1 (4.6 to 34).³¹⁹ About 54% of patients had local adverse events with capsaicin, compared with 15% with placebo (relative risk 3.6, 95% CI 2.6 to 5.0). Withdrawals due to adverse events were also significantly more likely with capsaicin (13% vs. 3%, relative risk 4.0, 95% CI 2.3 to 6.8).

2718 An older systematic review was excluded because it appears outdated.³²⁰

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Chapter 4. Summary and Discussion

The table below summarizes the strength of evidence and results for each key question. Publication bias is an issue for all of these questions, because we do not know the complete details or results of unpublished trials submitted to the FDA or trials that have been conducted but not published or submitted to the FDA

Table 28. Strength of evidence by key question

Key Question	Level of Evidence	Conclusion
1a. What is the evidence for benefits and harms of treating osteoarthritis with oral medication(s)?		
Efficacy: Non-selective NSAID vs. non-selective NSAID	Non-selective NSAID vs. non-selective NSAID: <i>good</i> . Consistent evidence from several good-quality systematic reviews and published trials. Salsalate vs. aspirin. <i>Poor</i> . One short-term trial. Salsalate or aspirin vs. non-aspirin NSAIDs. <i>Poor</i> .	No difference in efficacy between various non-aspirin, non-selective NSAIDs or partially selective NSAIDs (meloxicam, nabumetone, etodolac). No difference between salsalate and aspirin in one short-term trial. There were no trials or eligible observational studies of salsalate or aspirin vs. non-aspirin NSAIDs.
Efficacy: COX-2 selective vs. non-selective NSAID	Good. Consistent evidence from many published trials	No difference.
Efficacy: COX-2 selective vs. COX-2 selective	Good. Consistent evidence from six published trials.	No clinically significant differences at comparable doses.
GI and CV safety: Rofecoxib	Good. One large published trial, multiple meta-analyses and systematic reviews of published and unpublished trials, multiple observational studies.	In the only large, long-term trial, rofecoxib at 50 mg daily significantly reduced symptomatic ulcers and serious ulcer complications compared with naproxen in patients with RA. For rofecoxib there was 1 fewer symptomatic ulcer for every 62 patients treated; one fewer serious GI complication for every 191; and one additional MI for every 333 patients. The overall rate of serious adverse events was higher with rofecoxib 50 mg than naproxen. A good-quality systematic review, observational studies, and results of a polyp prevention trial are consistent with these findings.

GI and CV safety: Celecoxib	Fair: Multiple meta-analyses and systematic reviews of mostly short-term published and unpublished trials, multiple observational studies.	In the only published large, long-term trial, celecoxib was no different than diclofenac or ibuprofen for complicated or symptomatic ulcers at the end of the trial. In subgroup analyses of patients not on aspirin, celecoxib was superior to ibuprofen but not to diclofenac for ulcer complications. There was no increase in the rate of cardiovascular events, though analyses were performed on truncated 6-month data. The overall rate of serious adverse events was similar to ibuprofen and diclofenac. Systematic reviews and other meta-analyses of primarily short-term, unpublished data and lower doses found that celecoxib was superior to non-selective NSAIDs for ulcer complications. Observational studies are generally consistent with the short-term trials. However, a long-term polyp prevention trial found an increased, dose-dependent risk of myocardial infarction with celecoxib compared with placebo.
GI and CV safety: Valdecoxib	Fair: Fair quality meta-analyses of published and unpublished trials	Valdecoxib was associated with a lower short-term risk of upper GI complications compared with non-selective NSAIDs. There was one fewer upper GI complication with valdecoxib for every 78 patients treated for 3 to 6 months. There was no association between valdecoxib and myocardial infarction in primarily short-term chronic pain trials. However, two short-term trials in a high-risk post-coronary artery surgery setting found that valdecoxib was associated with a two- to three-fold higher risk of cardiovascular events compared with placebo.
GI and CV safety: Partially selective NSAIDs	GI safety: Fair for meloxicam (short-term RCTs, meta-analyses, observational studies); poor for nabumetone and	GI safety: Meloxicam had no advantage in GI risk relative to other NSAIDs; evidence was insufficient to make reliable judgments about GI safety of nabumetone and etodolac

	etodolac CV safety: Poor for all; two observational studies for meloxicam	CV safety: No increased risk associated with meloxicam relative to non-selective NSAIDs; no evidence for nabumetone and etodolac
GI and CV safety: Non-selective NSAIDs	Good for GI safety. Consistent evidence from many published trials, systematic reviews, and observational studies Fair for CV safety. No large, long-term controlled trials. Almost all evidence from observational studies	No clear difference in GI safety between non-selective NSAIDs at commonly used doses. Naproxen was associated with a modest cardiovascular protective effect compared with other NSAIDs in a good-quality systematic review of observational studies, but methodological issues could have affected the results. CV safety of other non-aspirin NSAIDs is not clear. A large systematic review of RCTs addressing this issue has not yet been published.
GI and CV safety: Aspirin	Fair. Many trials and systematic reviews, but almost exclusively in patients receiving aspirin for cardiovascular prophylaxis.	Aspirin is associated with a lower risk of thromboembolic events and a higher risk of GI bleeds when given in prophylactic doses. Insufficient evidence to assess safety of aspirin in therapeutic doses compared with non-aspirin NSAIDs.
GI and CV safety: Salsalate	Poor. Almost all data are from fair-to-poor quality observational studies in patients with rheumatoid arthritis.	Salsalate was associated with a lower risk of adverse events as defined using broad composite endpoints in older, poor-quality observational studies. In a more recent observational study, salsalate had a similar rate of complications compared with other NSAIDs. Almost no data is available on CV safety.
Mortality	Fair. Individual trials not large enough to detect differences in mortality. One meta-analysis of celecoxib using unpublished information, and one fair-quality observational study of non-selective NSAIDs.	No difference between celecoxib and non-selective NSAIDs, but few events. In one cohort study, nabumetone was associated with lower all-cause mortality compared with diclofenac and naproxen, but this finding has not been replicated.
HTN, CHF, edema, and renal function	Fair. Multiple systematic reviews, clinical trials, and observational studies, but	One major trials and several observational studies suggest increased risks for heart failure with rofecoxib,

	analyses limited by inconsistent reporting of results and probable publication bias	but these are not conclusive. Rofecoxib also associated with more cardiorenal events than celecoxib in three head-to-head trials of high-risk patients, but nonequivalent dosing limits interpretation of these results. No clear differences between celecoxib, partially selective, and non-selective NSAIDs.
Hepatotoxicity	Good. Systematic reviews of multiple trials and observational studies	Clinically significant hepatotoxicity was rare. Several NSAIDs associated with high rates of hepatotoxicity have been removed from the market. Among currently marketed NSAIDs, diclofenac was associated with a higher rate of liver-related discontinuations compared with placebo (2.17%).
Tolerability	Good for coxibs and non-selective NSAIDs (consistent results from multiple systematic reviews); fair for partially selective NSAIDs and aspirin (few meta-analyses and short-term trials)	Relative to non-selective NSAIDs, coxibs and partially selective NSAIDs were at least as well tolerated and aspirin was less tolerated; no differences among coxibs or among non-selective NSAIDs
Acetaminophen	Good overall. Consistent results from multiple systematic reviews for efficacy and GI adverse events. Poor for cardiovascular safety (no evidence) and fair for renal safety (observational studies)	Acetaminophen is modestly inferior to NSAIDs for pain and function. Acetaminophen is superior to NSAIDs for GI side effects (clinical trials data) and GI complications (observational studies). Acetaminophen may be associated with modest increases in blood pressure and renal dysfunction (observational studies). Acetaminophen is not associated with an increased risk of hepatotoxicity at therapeutic doses.
Glucosamine and chondroitin	Fair. Inconsistent evidence from clinical trials. Most promising results have been obtained in trials funded by a European manufacturer of pharmaceutical grade glucosamine not approved in the U.S.	Glucosamine was superior to oral NSAIDs and placebo in trials evaluating pharmaceutical grade glucosamine and funded by its manufacturer. Other trials found no difference between glucosamine and placebo or glucosamine and oral NSAIDs. Final results of an NIH funded trial in the U.S. are pending. Chondroitin was superior to placebo, but trials were flawed.

1b. How do these benefits and harms change with dosage and duration of treatment, and what is the evidence that alternative dosage strategies, such as intermittent dosing and drug holidays, affect the benefits and harms of oral medication use?	Good for safety (consistent evidence from multiple clinical trials and observational studies), no evidence for alternative dosage strategies.	Risk of GI bleeding increases with higher doses of non-selective NSAIDs. Effects of dose and duration are somewhat inconsistent. Celecoxib was most effective for GI safety at 6 months and not after longer follow-up in the CLASS trials. Dose-dependent CV risk of celecoxib has been observed in a long-term prevention trial. CV risk of rofecoxib became most apparent after 8 months in VIGOR and after 18 months in the APPROVe prevention trial. Most, but not all, observational studies suggest a dose-dependent effect of rofecoxib on MI risk.
Key Question 2. Are there clinically important differences in the harms and benefits of oral treatments for osteoarthritis for certain demographic and clinical subgroups?		
Demographic subgroups including age, sex, and race	Good (age, sex) Poor (race)	Most studies included a majority of women. The risks of GI and CV events increase in older patients. The data that selective COX-2 inhibitors are safe and efficacious in different racial groups have been presented to the FDA, but no clear differences have been described in the peer-reviewed literature.
Pre-existing disease including history of previous bleeding due to NSAIDs or peptic ulcer disease; hypertension, edema, ischemic heart disease, and heart failure	Previous bleeding: Good Hypertension, edema: Fair Ischemic Heart Disease: Poor (no comparative studies) Heart failure: Fair	Risk of bleeding is higher in patients with prior bleeding or PUD. Two trials found high rates of recurrent ulcer bleeding in patients randomized to celecoxib versus a non-selective NSAID + PPI. Risk of CV and renal events is higher in patients with cardiac and renal co-morbidities. In a single observational study that examined mortality, rofecoxib and non-selective NSAIDs were associated with higher rates of death and recurrent heart failure than celecoxib.
Concomitant anticoagulant	Fair overall: Primarily	Concomitant use of anticoagulants and

use	observational studies	non-selective NSAIDs increase the risk of GI bleeding three- to six-fold. Reliable conclusions about the safety of selective NSAIDs in the setting of anticoagulation could not be drawn from flawed observational studies. Warfarin plus aspirin (prophylactic doses) increased risk of bleeding compared with warfarin alone in patients with indications for antithrombotic prophylaxis. Acetaminophen can increase INR levels, but effects on bleeding rates have not been studied.
Concomitant aspirin use	<p>Good for GI safety: Consistent evidence from clinical trials and observational studies</p> <p>Fair for CV safety: Subgroup analyses from few trials, few observational studies</p>	Concomitant use of aspirin attenuates or eliminates the GI benefits of selective NSAIDs. Concomitant low-dose aspirin increased the rate of endoscopic ulcers by about 6% in patients on celecoxib and those on non-selective NSAIDs in one meta-analysis. In one trial, rofecoxib plus low-dose aspirin and ibuprofen were associated with a similar risk of endoscopic ulcers (16-17%); both were significantly higher than placebo (6%) or aspirin alone (7%). Effects of concomitant aspirin on CV risk associated with NSAIDs are unclear.
3. What is the evidence that the gastrointestinal harms of NSAID use are reduced by co-prescribing of H2-antagonists, misoprostol, or PPIs?	Good: Consistent evidence from good-quality systematic reviews and numerous clinical trials	Misoprostol and PPIs offer some advantages over double-dose H2-antagonists. PPIs are associated with the lowest rates of endoscopically detected <i>duodenal</i> ulcers. Misoprostol is associated with similar rates of endoscopically detected <i>gastric</i> ulcers as PPIs. While misoprostol offers the advantage of being the only gastroprotective agent to reduce rates of clinical GI events, this clinical advantage is accompanied by an increased risk of GI-related adverse event withdrawals.
4. What are the benefits and safety of treating		

osteoarthritis with oral medications as compared with topical preparations?		
Topical NSAIDs: efficacy	Good: Consistent evidence for selected topical NSAIDs from clinical trials	Topical NSAIDs are similar to oral NSAIDs for efficacy. Topical diclofenac is the best studied, though many trials evaluated a formulation using a DMSO carrier that is not available in the U.S. Topical ibuprofen was superior to placebo in several trials.
Topical NSAIDs: safety	Good: Consistent evidence from trials and systematic reviews and observational studies	Topical NSAIDs are associated with increased local adverse events compared with oral NSAIDs. Total adverse events and withdrawal due to adverse events are similar. Topical NSAIDs are superior for GI events, including severe events, and changes in hemoglobin (data from one good-quality trial).
Topical salicylates: (including capsaicin)	Fair: Only placebo-controlled trials, many of which were flawed	Topical salicylates were no better than placebo in higher-quality trials. Topical capsaicin was superior to placebo (NNT 8.1), but associated with increased local adverse events and withdrawals due to adverse events.

Discussion

This report provides a comprehensive summary of the comparative efficacy and safety of oral nonsteroidal anti-inflammatory drugs (NSAIDs) (selective, non-selective, aspirin, and salsalate), acetaminophen, certain over-the-counter supplements (chondroitin and glucosamine), and topical agents (NSAIDs and rubefacients, including capsaicin) that are commonly used for pain control and improvement of functional status in patients with osteoarthritis. At this time, no drug or supplement is known to modify the course of disease.

Evidence regarding the benefits of oral NSAIDs from primarily short-term randomized controlled trials is abundant and demonstrates no clear, consistent differences for relieving pain or other osteoarthritis-related symptoms, or for superior tolerability. On the other hand, much of the uncertainty and confusion regarding NSAIDs centers on their comparative safety.

The trade-offs between reduced GI risk and increased CV harms was first clearly observed in VIGOR. In this trial, rofecoxib 50 mg daily significantly reduced symptomatic ulcers (NNT=62) and serious ulcer complications (NNT=191) compared with naproxen in patients with rheumatoid arthritis.¹⁸ However, the GI-protective effects were accompanied by a more than four-fold increase in myocardial infarctions, or one additional myocardial infarction for every 333 patients treated with rofecoxib. When considering all “serious” adverse events,

moreover, rofecoxib was not associated with any clear benefit compared with naproxen.¹¹⁵

Rofecoxib became the focus of intense scrutiny following publication of VIGOR. Findings from a good-quality systematic review¹²⁵ and multiple observational studies¹³⁴⁻¹⁴⁷ were largely consistent with the increased CV risk observed in VIGOR. Rofecoxib was voluntarily withdrawn from the market in 2004, after a long-term placebo-controlled polyp prevention trial also demonstrated an increase in cardiovascular risk.¹⁹² Valdecoxib was also withdrawn from the market, leaving celecoxib the only selective NSAID currently available in the U.S.

The same concerns about the overall safety of rofecoxib have been directed at celecoxib. The evidence regarding the relative GI and CV safety of celecoxib, however, is less clear. In CLASS, the largest published study of GI complications, celecoxib was not significantly different than diclofenac or ibuprofen for either ulcer complications or myocardial infarctions by the end of follow-up.¹⁰⁰ Like the VIGOR trial, re-analysis of all serious adverse events in CLASS found no significant advantage for celecoxib.¹⁰⁰ Systematic reviews and other meta-analyses of primarily short-term and frequently unpublished data, on the other hand, found that celecoxib (primarily at lower doses than were used in CLASS) was associated with lower rates of ulcer complications than were non-selective NSAIDs,^{66, 121} though again with no increased risk of myocardial infarctions or thromboembolic cardiovascular events.^{66, 122, 128} These findings would appear to suggest an overall net benefit for celecoxib compared with non-selective NSAIDs. Longer-term observational studies are generally consistent with this inference in that celecoxib was consistently GI protective^{135, 154} or neutral¹³⁴ and was never associated with higher risks of CV events relative to non-selective NSAIDs.^{139, 140, 145, 152} Additionally, celecoxib was consistently associated with lower risks of serious GI¹³⁵ and CV events^{139, 140, 152} than rofecoxib in several observational studies.

An important drawback of the observational studies, however, is that they largely focused on individual adverse events in isolation. More informative analyses of the overall trade-off between risks and benefits would consider all serious adverse events. Our re-analysis and additional modeling of results from three studies^{135, 142, 155} reporting myocardial infarctions, heart failure hospitalizations, and gastrointestinal bleeding in the same elderly Canadian population suggests that celecoxib may confer net advantages in terms of the number of these events compared with rofecoxib and non-selective NSAIDs, but additional studies on original data are needed to confirm this finding in other settings.

The main discordant piece of evidence regarding celecoxib comes from a recent placebo-controlled polyp prevention trial of celecoxib (APC) that was terminated after 33 months because of an apparently dose-dependent higher rate of cardiovascular events in the celecoxib arms.¹²⁹ In APC, the increase in rates of events associated with celecoxib relative to placebo was only observed after 9 months of follow-up. However, preliminary data from two other placebo-controlled prevention trials found no increased cardiovascular risk.^{130, 131} It is not clear why the results of these trials differed from the APC trial, though full publication of results may prove to be more informative. The results of APC, however, underscore the importance of analyzing longer-term data and assessing dose effects in future trials of NSAIDs.

At this time, there is insufficient evidence to reliably judge the relative cardiovascular safety of the partially selective NSAIDs nabumetone, diclofenac, and meloxicam, or different non-selective NSAIDs. A systematic review that analyzed published and unpublished data on cardiovascular safety from more than 130 trials of NSAIDs was not yet available for this review, but should directly address this issue. For GI safety, no clear advantage for any particular partially selective or non-selective NSAIDs has been demonstrated.

Topical NSAIDs may offer the advantages of local analgesic and anti-inflammatory effects without the systemic side effects of oral administration. They would probably be most useful in patients with a limited number of affected joints. Although topical NSAIDs appear comparable to oral NSAIDs for pain relief in several trials, the most convincing evidence comes from a recent trial that evaluated a proprietary formulation of diclofenac with DMSO that has not been FDA-approved.³⁰⁸ Topical NSAIDs appear safer than oral NSAIDs for GI safety, but data on comparative cardiovascular risks are not available. The relative benefits of topical rubefacients compared with topical or oral NSAIDs has not been adequately studied, and other than for capsaicin, there is insufficient evidence to prove that topical rubefacients are superior to placebo for osteoarthritis.

Acetaminophen is often considered an attractive alternative to NSAIDs because of its perceived safety profile. It was associated with GI-protective effects relative to non-selective NSAIDs,^{212, 214} though at the expense of modestly inferior efficacy.²¹⁷ More evidence is needed to compare the effects of acetaminophen and NSAIDs on other important adverse events such as renal dysfunction, blood pressure, and heart failure. Aspirin is another attractive alternative to NSAIDs because of its cardiovascular protective effect. However, nearly all of the evidence on cardiovascular and GI safety of aspirin is from trials using lower preventative rather than anti-inflammatory doses.

Glucosamine and chondroitin are widely available as over-the-counter supplements. The highly variable content of currently available products, however, remains a significant issue in the U.S. Further, nearly all of the trials demonstrating benefits of glucosamine have been conducted using pharmaceutical grade preparations not currently available in the U.S.²³⁰ While these agents appear to be safe in the short term, high-quality, long-term safety data are not yet available. Compared with the evidence for glucosamine, the evidence for chondroitin appears less promising.

Strategies to reduce the risk of GI complications in patients taking NSAIDs include co-prescription of misoprostol, standard- or double-dose H2 blockers, or PPIs. All of these strategies are effective in reducing the risk of NSAID-associated *endoscopic* gastric and duodenal ulcers relative to use of non-selective NSAIDs alone. Misoprostol (RR 0.36, 95% CI 0.20 to 0.67) and PPIs (RR 0.09, 95% CI 0.02 to 0.47) also reduced NSAID-associated symptomatic ulcers.²⁶⁵ Further, misoprostol is the only agent proven to decrease risk of clinical GI events, but is associated with an increased risk of withdrawals due to nausea, diarrhea, and/or abdominal pain.²⁸⁸ In high-risk patients (those with a recent bleed), non-selective NSAIDs and the combination of a non-selective NSAID plus a PPI were both associated with similar, high rates of recurrent bleeding.^{246, 247}

In summary, each of the analgesics evaluated in this report was associated with a unique set of risks and benefits. The role of selective and non-selective oral NSAIDs and alternative agents will continue to evolve as additional information emerges. At this time, although the amount and quality of evidence varies, no currently available analgesic reviewed in this report was identified as offering a clear overall advantage compared with the others, which is not surprising given the complex trade-offs between the many benefits (pain relief, improved function, improved tolerability, and others) and harms (cardiovascular, renal, GI, and others) involved. In addition, individuals are likely to differ in how they prioritize the importance of the various benefits and harms of treatment. Adequate pain relief at the expense of a small increase in CV risk, for example, could be an acceptable trade-off for many patients. Others may consider even a marginal increase in CV risk unacceptable. Factors that should be considered

2842 when weighing the potential effects of an analgesic include age (older age being associated with
2843 increased risks for bleeding and cardiovascular events), co-morbid conditions, and concomitant
2844 medication use (such as aspirin and acetaminophen). As in other medical decisions, choosing the
2845 optimal analgesic for an individual with osteoarthritis should always involve careful
2846 consideration and thorough discussion of the relevant trade-offs.
2847

Chapter 5. Future Research

- Nearly all of the clinical trials reviewed in this report were “efficacy” trials conducted in ideal settings and selected populations. “Pragmatic” and other clinical trials of effectiveness would be very valuable for learning the outcomes of different analgesic interventions in real-world settings.
- To assess the cardiovascular safety of non-selective NSAIDs, trials comparing different non-selective NSAIDs or other analgesics are needed to validate the findings of observational studies on the risk for cardiovascular events. Naproxen in particular may have a different cardiovascular safety profile than other NSAIDs and should be investigated in long-term, appropriately powered trials. The CV risk associated with the partially selective NSAIDs meloxicam, nabumetone, and diclofenac has not been well studied and should also be investigated in appropriate trials.
- Large observational studies assessing the safety of NSAIDs have been helpful for assessing comparative benefits and harms, but have either focused on GI risk or CV risk, rather than both. Observational studies that take a broader view, examining all serious adverse events, would be substantially more helpful for assessing the overall trade-offs between benefits and harms.
- The cardiovascular risks and GI benefits associated with different COX-2 selective NSAIDs may vary. Large, long-term trials with active and placebo-controlled arms would be needed to assess the safety and benefits of any new selective NSAID.
- Dose and duration must be better assessed in meta-analyses of the risks associated with selective COX-2 inhibitors, as the cardiovascular risks have occurred primarily at high doses and with prolonged use .
- Large, long-term trials of the GI and cardiovascular safety associated with full-dose aspirin, salsalate, or acetaminophen compared with non-aspirin NSAIDs or placebo are lacking.
- More studies evaluating differential safety or efficacy in specific subgroups as defined by gender and race are needed.
- Genetic testing could theoretically help predict patients who are at higher risk of cardiovascular complications from selective COX-2 inhibitors because of differences in the COX-2 gene promoter or other genes. This is a potentially promising area of future research.
- The effects of alternative dosing strategies such as intermittent dosing or drug holidays have not been assessed. Studies evaluating the benefits and risks associated with such strategies compared with conventional dosing could help clarify the effects of these alternative dosing strategies.

- Most trials showing therapeutic benefits from glucosamine were conducted using pharmaceutical grade glucosamine not available in the U.S. and may not be applicable to currently available over-the-counter preparations. Large trials comparing currently available over-the-counter preparations with oral NSAIDs are needed, as these preparations are likely to remain available even if the FDA approves a pharmaceutical grade glucosamine product.
- High-quality trials of chondroitin are lacking.
- No topical NSAIDs are FDA-approved in the U.S., yet compounding of NSAIDs into topical preparations is widely available. Although recent trials of topical NSAIDs are promising, most have been conducted using a proprietary formulation of diclofenac with DMSO. A UK trial of topical versus oral ibuprofen is currently in progress and will help further clarify the benefits and safety of topical versus oral NSAIDs. However, large observational databases may be required to adequately assess cardiovascular risk.

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